[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

Amine Oxides. X. Thermal Decomposition of the N-Oxides and Methohydroxides of *cis*- and *trans*-N,N-Dimethyl-2-aminocyclohexanol and *cis*- and *trans*-N,N-Dimethyl-2-aminocyclooctanol[1,2]

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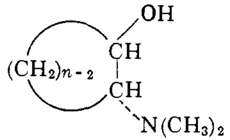
Pyrolysis of the N-oxides of *trans*-N,N-dimethyl-2-aminocyclohexanol and -cyclooctanol gave mixtures of the corresponding 2-cycloalken-1-ols and cycloalkanones in the ratio of 18:1 and 20:1, respectively. *cis*-N,N-Dimethyl-2-aminocyclohexanol N-oxide, on pyrolysis, gave 2-cyclohexen-1-ol as the sole neutral product, whereas the corresponding cyclooctanol derivative yielded a mixture of 2-cycloocten-1-ol (30%) and cyclooctanone (6%). In the N-oxide pyrolyses varying amounts of oxazolidines also were formed. Thermal decomposition of the methohydroxides of *trans*-N,N-dimethyl-2-aminocyclohexanol and its eight-membered homolog gave only cyclohexene oxide and *cis*-cyclooctene oxide, respectively. The *cis* isomers, under these conditions, yielded mixtures of the corresponding 2-cycloalken-1-ols and cycloalkanones (in the ratio of 1:2 and 1:7, respectively) as well as methylation products of these ketones and allylic alcohols. *cis*-N,N-Dimethyl-2-methoxycyclohexylamine and its eight-membered homolog, respectively, were found among the basic products of these pyrolyses. No evidence was found for a transannular reaction in the pyrolyses of the N-oxides and methohydroxides of the eight-membered cyclic aminoalcohols.

The method of converting tertiary amines to olefins by the thermal decomposition of their N-oxides has recently been applied to a number of aliphatic and alicyclic amines,[4] and the results have been compared with those obtained in the Hofmann elimination reaction. This study has now been extended to include β-aminoalcohols. It is intended to investigate the course of these elimination reactions in amines containing various other functional groups.

The compounds investigated were the stereoisomeric pairs of N,N-dimethyl-2-aminocyclohexanols (Ia and IIa) and N,N-dimethyl-2-aminocyclooctanols (Ib and IIb). The former were chosen because of their well-known stereochemistry, while the *cis* and *trans* isomers of the eight-membered cyclic aminoalcohol were included because of the possibility that the elimination reactions might take an abnormal course in this case. Whereas reactions of medium-sized cyclic compounds which involve carbonium ions, carbenes and free radicals as intermediates frequently do not proceed as predicted by classical theories, few cases have been observed so far where such anomalies occur in pyrolytic reactions.[5]



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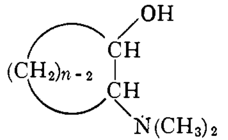

II

a, $n = 6$
b, $n = 8$

trans - N,N - Dimethyl - 2 - aminocyclohexanol (Ia) was prepared by treatment of *trans*-2-chlorocyclohexanol[6] with dimethylamine.[7] *trans*-2-Aminocyclohexanol[8] was isomerized to the *cis* epimer by treatment of the N-benzoyl derivative with thionyl chloride followed by hydrolysis of the intermediate *cis*-oxazoline.[9] The *cis*-aminocyclohexanol so obtained was methylated by the Clarke–Eschweiler method, forming *cis*-N,N-dimethyl-2-aminocyclohexanol (IIa). Since it was feared that epimerization to the more stable *trans* isomer might occur during the last stage of this preparation, IIa was also synthesized by lithium aluminum hydride reduction[10] of the methiodide of IIa obtained by direct quaternization of *cis*-2-aminocyclohexanol. The aminoalcohols obtained by the two methods had identical melting points and infrared spectra. Separation of the two isomers Ia and IIa by gas chromatography could not be effected; however, the fact that no cyclohexene oxide was detected in the products of the pyrolysis of the methohydroxide of IIa indicates that the *cis*-aminoalcohol was not contaminated by the *trans* isomer, which yields the epoxide as the sole product of this reaction (see below). The finding that the Clarke–Eschweiler methylation proceeds without epimerization of the α-carbon atom has since been substantiated in a number of cases.[10] *trans*-N,N-Dimethyl-2-aminocyclooctanol (Ib) was prepared by the addition of dimethylamine to *cis*-cyclooctene oxide.[11] The *cis* isomer IIb was obtained by the sequence employed for the six-membered cyclic homolog except for one modification. When *cis*-2-aminocyclooctanol was subjected to the Clarke–Eschweiler methylation, *cis*-1,2-hexamethylene-N-methyloxazolidine (IVb) was obtained instead of the expected *cis* - N,N - dimethyl - 2 - aminocyclooctanol (IIb). The latter was finally prepared by heating the oxazolidine IVb with concentrated hydrochloric acid in the presence of excess formaldehyde and formic acid. The stability of the oxazolidine IVb is remarkable in view of the fact that its six-membered homolog IVa is very sensitive to acid. The isomeric eight-membered amino-

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[1] Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-19-020-ORD-4542.

[2] Paper IX, *J. Am. Chem. Soc.*, **83**, 3854 (1961).

[3] National Institutes of Health Fellow, 1960–1961.

[4] For a summary see A. C. Cope and E. R. Trumbull, "Organic Reactions," Vol. XI, John Wiley and Sons, Inc., New York, N. Y., 1960, pp. 317–493.

[5] A. C. Cope and M. M. Martin, to be published.

[6] M. S. Newman and C. A. VanderWerf, *J. Am. Chem. Soc.*, **67**, 233 (1945).

[7] A. E. Osterberg and E. C. Kendall, *ibid.*, **43**, 1370 (1921).

[8] N. A. B. Wilson and J. Read, *J. Chem. Soc.*, 1269 (1935).

[9] W. S. Johnson and E. N. Schubert, *J. Am. Chem. Soc.*, **72**, 2187 (1950).

[10] A. C. Cope, E. Ciganek, L. J. Fleckenstein and M. A. P. Meisinger, *ibid.*, **82**, 4651 (1960).

[11] M. A. P. Meisinger, Ph.D. Thesis, Massachusetts Institute of Technology, 1956.

TABLE I

PRODUCTS OBTAINED FROM AMINE OXIDES AND METHOHYDROXIDES OF N,N-DIMETHYL-2-AMINOCYCLOALKANOLS

Pyrolysis				Neutral products,[a] %			Basic products,[a,b] %	
No.	Type	Amino-alcohol	Temp. of decomp., °C.	2-Cyclo-alken-1-ol	Cyclo-alka-none	Other	Recovd. amino-alcohol	Other
1	Hofmann	Ia	115–140	0	0	Cyclohexene oxide, 74	0	0
2	N-Oxide	Ia	150–160	9	0.5	0	17	*trans*-Hexahydro-N-methylbenzoxazoline (IIIa), 41
3	N-Oxide	Ia	170–190	56	3	0	4	IIIa, 9
4	Hofmann	IIa	150–155	3	7	3-Methoxycyclohexene, 2 1-Methoxycyclohexene, 0.3	34	*cis*-N,N-Dimethyl-2-methoxy-cyclohexylamine (Va), 17
5	N-Oxide	IIa	170–230[c]	30	0	0	10	*cis*-Hexahydro-N-methylbenzoxazoline (IVa), 23
6	Hofmann	Ib	130–150	0	0	*cis*-Cycloöctene oxide, 82	0	0
7	N-Oxide	Ib	110–135	61	3	0	7	*trans*-1,2-Hexamethylene-N-methyloxazolidine (IIIb), 1
8	Hofmann	IIb	130–135	2	15	*cis*-Cycloöctene oxide, 0.1[d] 3-Methoxycycloöctene, 8 2-Methylcycloöctanone, 2 2,2-Dimethylcycloöctanone, 0.6	13	*cis*-N,N-Dimethyl-2-methoxy-cycloöctylamine (Vb), 5
9	N-Oxide	IIb	120–145	30	6	0	7	*cis*-1,2-Hexamethylene-N-methyloxazolidine (IVa), 4

[a] The yields are averages of two decompositions. They are based on the aminoalcohols for the N-oxide pyrolyses, and on the methiodides for the Hofmann elimination reactions. [b] Only products other than N,N-dimethylhydroxylamine and trimethylamine are listed. [c] Only part of the N-oxide decomposed since a considerable amount sublimed. [d] Probably formed from a small amount of Ib in IIb.

alcohols Ib and IIb could not be separated by gas chromatography; however, in the mixture of neutral products obtained from the pyrolysis of the methohydroxide of IIb, 0.1% of *cis*-cycloöctene oxide was detected. This fact indicates the presence of a small amount of the *trans*-aminoalcohol in the *cis* isomer, since the former yields the epoxide as the sole product of this reaction.

The N-oxides and methohydroxides were prepared and pyrolyzed. The products were analyzed by gas chromatography and identified by their infrared spectra or preparation of derivatives. The results are compiled in Table I. Heating to unusually high temperatures was necessary to decompose the N-oxides of the two six-membered cyclic aminoalcohols. This circumstance probably reflects the reluctance of the cyclohexane ring to give up the preferred chair conformation in favor of one in which the N-oxide group and the β-hydrogen atom become coplanar as required for the five-membered cyclic transition state.[4] Strong hydrogen bonding between the hydroxyl group and the oxygen atom of the N-oxide function may also increase the difficulty of the elimination. The formation of 2-cyclohexen-1-ol as the sole neutral product in the pyrolysis of the N-oxide of IIa is in accord with the *cis* mechanism formulated for this elimination reaction.[4] In the pyrolysis of the N-oxide of *cis*-N,N-dimethyl-2-aminocyclooctanol (IIb) a small amount of cycloöctanone is also formed besides the expected 2-cycloöcten-1-ol; this fact may be explained by considering the greater flexibility of the eight-membered ring as contrasted to the rigid six-membered ring system. The pyrolysis of the N-oxide of Ia proceeded with the preferential formation, by a factor of *ca.* 18, of 2-cyclohexen-1-ol, the product of elimination of the hydrogen atom on C_3; similarly, the pyrolysis of the N-oxide of Ib proceeded with the preferential formation, by a factor of *ca.* 20, of 2-cycloöcten-1-ol. In the transition state for the elimination of the other hydrogen atom (the one on C_1) leading to the enol of cyclohexanone or cycloöctanone the hydroxyl group is forced into an eclipsed conformation with a hydrogen atom on C_2 which may account for the preferential elimination in the other direction. A similar explanation has been advanced to account for the ratio of olefins formed in the pyrolysis of the N-oxide of N,N-dimethylmenthylamine.[12] The ratio of basic to neutral products in the pyrolysis of *trans*-N,N-dimethyl-2-aminocyclohexanol N-oxide seems to depend on the temperature of the decomposition, higher temperature favoring normal *cis* elimination with the formation of neutral products. A possible mechanism that would account for the unexpected formation of the oxazolidines IIIa, IIIb, IVa and IVb in the pyrolysis of the N-oxides of Ia, Ib, IIa and IIb, respectively, is outlined in eq. 1.[13]

Cyclohexene oxide together with *trans*-1,2-cyclohexanediol have been isolated previously[8,14] from the decomposition of *trans*-N,N-dimethyl-2-aminocyclohexanol methohydroxide. The glycol, which most likely arises from cyclohexene oxide in a secondary reaction, was not found in the present study. The configuration of the aminoalcohols Ia and Ib with the two functional groups in *trans* relationship to each other is arranged favorably for backside displacement of the quaternary ammonium group by the hydroxyl group which in the strongly basic reaction medium probably exists largely as the alkoxide ion. Formation of cyclohexene oxide and *cis*-cycloöctene oxide, respectively, is therefore the only course of reaction observed. In the methohydroxide of the *cis*

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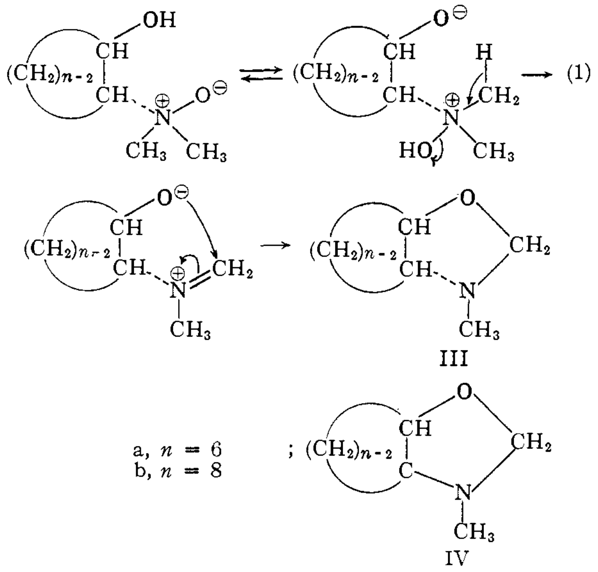
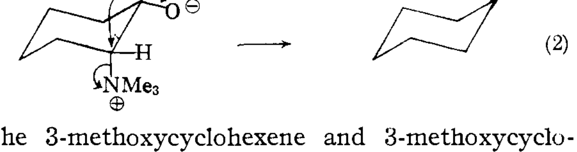
(12) A. C. Cope and E. M. Acton, *J. Am. Chem. Soc.*, **80**, 355 (1958).

(13) A similar mechanism was recently proposed for the Polonowsky reaction by R. Huisgen, F. Bayerlein and W. Heydkamp, *Chem. Ber.*, **92**, 3223 (1959).

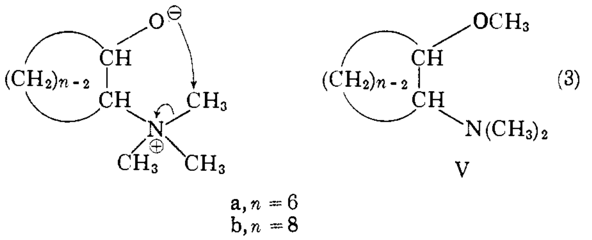
(14) H. W. Bersch and G. Hübner, *Arch. Pharm.*, **289**, 673 (1956).



isomers IIa and IIb attainment of the transition state leading to the (unknown) *trans*-cyclohexene oxide and *trans*-cycloöctene oxide, respectively, with the hydroxyl group *anti* and coplanar to the quaternary ammonium group is obviously prevented by the excessive strain associated with such a conformation.[15] The small amounts of neutral components isolated in these cases therefore arise by the normal mechanism of the Hofmann elimination reaction, namely an E$_2$-elimination involving the two *trans*-β-hydrogen atoms on C$_1$ and C$_3$ giving rise to the enol form of the cycloalkanone and 2-cycloalken-1-ol, respectively. The observed ratio of 2:1 of cyclohexanone to 2-cyclohexen-1-ol and of *ca.* 7:1 of cycloöctanone to 2-cycloöcten-1-ol is somewhat surprising since due to the proximity of the alkoxide ion the hydrogen atom on C$_1$ would be expected to be less acidic and also less easily attacked by the negatively charged hydroxyl ion than the hydrogen atom on C$_3$. The ketones probably do not arise by isomerization of the allylic alcohols since no conversion to cyclohexanone was observed when a sample of 2-cyclohexen-1-ol was heated with 45% aqueous tetramethylammonium hydroxide to 150° for thirty-five minutes (the products were unreacted allylic alcohol and its methyl ether, 3-methoxycyclohexene). A possible alternate mechanism for the formation of the cyclic ketones would involve a 1,2-hydride shift as shown in eq. 2 for cyclohexanone.



The 3-methoxycyclohexene and 3-methoxycyclooctene found among the neutral products of the Hofmann elimination reaction of IIa and IIb methohydroxides, respectively, most likely arise in a secondary methylation of the initially formed allylic alcohols by unreacted quaternary base. It was shown that 2-cyclohexen-1-ol was indeed partially methylated when subjected to simulated Hofmann conditions (see above). Similarly, cyclohexanone was found to give a small amount of its O-methylation product, 1-methoxycyclohexene, under these same conditions, and it is therefore likely that the trace of this enol ether found in the products of the pyrolysis of IIa methohydroxide was also formed in this way. In the products of the Hofmann elimination of IIb methohydroxide, only C-alkylation products of cycloöctanone (2-methylcycloöctanone and 2,2-dimethylcycloöctanone) were detected. The main basic products of the pyrolyses of the methohydroxides of *cis*-N,N-dimethyl-2-aminocyclohexanol and *cis*-N,N-dimethyl-2-aminocycloöctanol were the recovered aminoalcohols IIa and IIb, respectively, which arise by attack of hydroxide ion on an N-methyl group. This frequently observed side reaction in Hofmann eliminations probably also accounts for the formation of the methoxyamines Va and Vb, since the *cis* configuration is favorable for an *intramolecular* attack on an N-methyl group by the neighboring alkoxide ion as shown in eq. 3.



In conclusion it should be pointed out that the Hofmann elimination reaction and the N-oxide pyrolysis of the eight-membered aminoalcohols investigated in this study proceed without any contribution of a transannular reaction.

Experimental[16]

trans-N,N-Dimethyl-2-aminocyclohexanol (Ia).—Treatment of *trans*-2-chlorocyclohexanol[6] with dimethylamine in 1-butanol at 150°[7] gave Ia in 81% yield, b.p. 83° (12 mm.), n^{25}D 1.4638 (lit.[17] n^{20}D 1.4703). The methiodide, obtained in 92% yield after one crystallization from ethanol, melted at 217° (lit.[18] m.p. 217.0–217.5°). The picrate melted at 149° (lit.[18] m.p. 149–150°).

cis-2-Aminocyclohexanol Hydrochloride.—*trans*-2-Aminocyclohexanol[8] was converted[19] in 86% yield to its N-benzoyl derivative, m.p. 172–173° (lit.[9] m.p. 171–172°), which was cyclized according to the procedure of Johnson and Schubert.[9] The method was slightly changed in that

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[15] Recently M. Svoboda and J. Sicher, *Coll. Czech. Chem. Commun.*, **23**, 1540 (1958), reported the formation of *trans*-epoxides in the Hofmann elimination reactions of *cis*-N,N-dimethyl-2-aminocyclododecanol methohydroxide and the corresponding thirteen- and sixteen-membered homologs. Only cyclodecanone and possibly 2-cyclodecen-1-ol were formed from the ten-membered cyclic aminoalcohol derivative.

[16] Melting points are corrected and boiling points are uncorrected. The infrared spectra were obtained with a Perkin–Elmer model 21 recording spectrophotometer using a sodium chloride cell. Gas chromatographic analyses were carried out using 190 × 0.8-cm. Pyrex columns packed with 30% by weight of a stationary phase on 48–100 mesh Chromosorb (Johns–Manville). The stationary phases used were: (A) Silicone oil (Dow Corning 550) and (B) 1,2,3-tris-(2-cyanoethoxy)-propane. The samples were eluted with helium at 15 p.s.i. and detected with a thermal conductivity cell.

[17] H. D. Baldridge, Jr., W. J. McCarville and S. L. Friess, *J. Am. Chem. Soc.*, **77**, 739 (1955).

[18] F. E. King and D. Holmes, *J. Chem. Soc.*, 164 (1947).

[19] M. T. Leffler and R. Adams, *J. Am. Chem. Soc.*, **59**, 2252 (1937).

the excess thionyl chloride was removed by distillation under reduced pressure before the reaction mixture was poured into ether. Hydrolysis gave (after one crystallization from ethanol) *cis*-2-aminocyclohexanol hydrochloride in 54% yield (based on *trans*-2-aminocyclohexanol), m.p. 188–190° (lit.[9] m.p. 185.4–187.2°).

***cis*-N,N-Dimethyl-2-aminocyclohexanol (IIa).**—The *cis*-2-aminocyclohexanol hydrochloride was converted into the free base by addition of the theoretical amount of sodium methoxide to a suspension of the hydrochloride in methanol, followed by removal of the solvent from the filtered solution. The free aminoalcohol (m.p. 75–76°, lit.[9] m.p. 71–72°) was methylated using the Clarke–Eschweiler method.[10] *cis*-N,N-Dimethyl-2-aminocyclohexanol, b.p. 88° (16 mm.), m.p. 43–44° (lit.[20] b.p. 98° at 20 mm., m.p. 43–44°), was obtained in 84% yield. The infrared spectrum had no bands at 870, 945 and 1182 cm.$^{-1}$ which are characteristic of the *trans* isomer. Bands characteristic of the *cis* isomer are at 900, 914, 967, 989 and 1169 cm.$^{-1}$. The picrate melted at 169–170° (lit.[20] m.p. 162–163°), mixed melting point with the picrate of the *trans* isomer 132–145°. The methiodide, obtained in 88% yield after one crystallization from absolute ethanol, melted at 244° (lit.[17] m.p. 244–245°).

***trans*-N,N-Dimethyl-2-aminocyclooöctanol (Ib).**[21]—In a 300-ml. steel hydrogenation bomb were placed 21.2 g. of *cis*-cyclooctene oxide,[22] 60 ml. of anhydrous dimethylamine and 70 ml. of absolute ethanol. The bomb was rocked at 200° for 90 hr. The solution was washed from the bomb with ether and dried over magnesium sulfate. The solvents were removed and the residue distilled through a semi-micro column, yielding 23.8 g. (83%) of *trans*-N,N-dimethyl-2-aminocyclooöctanol (Ib), b.p. 125–127° (20 mm.), $n^{25}D$ 1.4769.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.20; H, 12.19; N, 8.24.

The methiodide, obtained in 83% yield after two crystallizations from ethanol, melted at 219.0–219.5°.

Anal. Calcd. for $C_{11}H_{24}INO$: C, 42.18; H, 7.72; N, 4.47; I, 40.52. Found: C, 42.09; H, 7.78; N, 4.31; I, 40.37.

***cis*-N,N-Dimethyl-2-aminocyclooöctanol (IIb).**—*trans*-2-Aminocyclooöctanol[23] was treated with benzoyl chloride according to the method of Leffler and Adams[19] to give *trans*-2-benzamidocyclooöctanol in 82% yield (after one crystallization from ethanol), m.p. 137.0–137.5°.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.93; H, 8.56; N, 5.71.

Cyclization of the *trans*-2-benzamidocyclooöctanol using the modified (see above) method of Johnson and Schubert[9] followed by hydrolysis and conversion to the free base gave a 62% yield of crude *cis*-2-aminocyclooöctanol, which was not further purified. The crude aminoalcohol (39 g.) was heated to 100° with 100 ml. of 98% formic acid and 130 ml. of 37% aqueous formaldehyde solution. After the evolution of carbon dioxide had stopped, the mixture was heated under reflux for 18 hr. Concentrated hydrochloric acid (45 ml.) was added to the cooled mixture, which was then concentrated to dryness under reduced pressure. The residue was taken up in 50 ml. of water and the solution was made strongly alkaline by the addition of sodium hydroxide. The resulting emulsion was extracted with five 150-ml. portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, the solvent was removed, and the residue was distilled through a short-path still at 114–125° (8 mm.). Gas chromatography of this product (column A[16] at 180°) showed it to be a mixture of 7% of the desired *cis*-N,N-dimethyl-2-aminocyclooöctanol (IIb) and 93% of *cis*-1,2-hexamethylene-N-methyloxazolidine (IVb, see below). A solution of 28 g. of this mixture in 40 ml. of 98% formic acid and 31 ml. of 37% aqueous formaldehyde was heated under reflux for 18 hr. The mixture was cooled to room temperature, 19 ml. of concentrated hydrochloric acid was added, and the mixture was slowly evaporated to dryness at atmospheric pressure. The product was isolated in the manner previously described. In this way 26.4 g. (57%) of *cis*-N,N-dimethyl-2-aminocyclooöctanol (IIb) was obtained, b.p. 94–97° (2 mm.), $n^{25}D$ 1.4879. Analysis of the liquid by gas chromatography (column A,[16] 180°) revealed no impurities.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.90; H, 12.30; N, 7.98.

The methiodide, obtained in 71% yield after two crystallizations from absolute methanol, melted at 180.5–181.0°.

Anal. Calcd. for $C_{11}H_{24}INO$: C, 42.18; H, 7.72; N, 4.47. Found: C, 42.05; H, 7.80; N, 4.73.

N-Oxides.—The aminoalcohols were oxidized with 30% aqueous hydrogen peroxide in methanol as described previously.[24] Aliquots of the amine oxide solutions were added to a small excess of picric acid in ethanol. The N-oxide picrates so obtained are listed below. The remaining amine oxide solutions were concentrated under reduced pressure and room temperature to sirups, which were then pyrolyzed as described below.

***trans*-N,N-Dimethyl-2-aminocyclohexanol N-Oxide Picrate.**—The N-oxide picrate of Ia was obtained in 97% yield after three crystallizations from methanol; m.p. 147–148°.

Anal. Calcd. for $C_{14}H_{20}N_4O_9$: C, 43.30; H, 5.19; N, 14.43. Found: C, 43.48; H, 5.30; N, 14.57.

***cis*-N,N-Dimethyl-2-aminocyclohexanol N-oxide picrate** was obtained in 87% yield after one crystallization from methanol; it melted at 131–133°.

Anal. Calcd. for $C_{14}H_{20}N_4O_9$: C, 43.30; H, 5.19; N, 14.43. Found: C, 43.21; H, 5.18; N, 14.48.

***trans*-N,N-Dimethyl-2-aminocyclooöctanol N-oxide picrate** melted at 122–124° after two crystallizations from ethanol.

Anal. Calcd. for $C_{16}H_{24}N_4O_9$: C, 46.15; H, 5.81; N, 13.46. Found: C, 46.37; H, 5.78; N, 13.71.

***cis*-N,N-Dimethyl-2-aminocyclooöctanol N-oxide picrate** melted at 138.0–139.5° after three crystallizations from methanol.

Anal. Calcd. for $C_{16}H_{24}N_4O_9$: C, 46.15; H, 5.81. Found: C, 45.90; H, 5.78.

Methohydroxides were prepared from the methiodides as previously described.[25]

Pyrolysis of N-Oxides and Methohydroxides.—Pyrolyses were carried out in a flask attached to two traps in series, the first cooled with Dry Ice–acetone, and the second with liquid nitrogen. The system was evacuated to 0.1–0.3 mm. pressure and the flask was heated slowly (stirred oil-bath) until pyrolysis began. The temperatures of decomposition are listed in Table I. The contents of the traps were taken up in pentane and ether, the combined solutions of the crude products were analyzed by gas chromatography (see below), and then extracted several times with cold 10% hydrochloric acid. The acid extracts were combined and washed with two portions of ether. The ether washings were combined with the original ether–pentane solution, washed with 5% sodium bicarbonate solution, and dried over magnesium sulfate. The solvents were removed and the residue was distilled through a semi-micro column, yielding the neutral component(s). The acid extracts were concentrated to dryness, and the residue was dissolved in water and made strongly basic by the addition of sodium hydroxide. The resulting emulsion was extracted several times with ether, the combined ether extracts were dried over potassium hydroxide pellets, the solvent was removed and the residue distilled through a semi-micro column, yielding the basic product(s).

Identification of Products. (A) **Products Obtained from the Aminocyclohexanols Ia and IIa.**—Gas chromatographic analyses of the neutral fractions was carried out using column B[16] at 120°, and of the basic fractions using column A[16] at 150–160°. The crude product mixtures from the pyrolyses (see above) were analyzed on both columns. Unless otherwise noted, the method used to isolate the neutral and basic fractions did not result in any change of the product composition. Preparative gas chromatography was used to isolate the individual compounds from the neutral and basic fractions. The samples of cyclohexene

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[20] M. Mousseron, J. Jullien and Y. Jolchine, *Bull. soc. chim. France*, 757 (1952).

[21] This experiment was carried out by M. A. P. Meisinger; see ref. 11.

[22] A. C. Cope, S. W. Fenton and C. F. Spencer, *J. Am. Chem. Soc.*, **74**, 5884 (1952).

[23] M. Mousseron and R. Granger, *Bull. soc. chim. France*, 850 (1947).

[24] A. C. Cope and E. Ciganek, *Org. Syntheses*, **39**, 40 (1959).

[25] A. C. Cope, N. A. LeBel, H. H. Lee and W. R. Moore, *J. Am. Chem. Soc.*, **79**, 4720 (1957).

oxide,[26] 2-cyclohexen-1-ol,[27] 3-methoxycyclohexene[28] and cyclohexanone obtained from pyrolyses no. 1–5 had infrared spectra identical with those of authentic samples (to which the reference numbers refer). The acid-sensitive 1-methoxycyclohexene (from pyrolysis no. 4) was detected only in the crude reaction products; it had a retention time on gas chromatography using two different columns (A[16] at 90° and B[16] at 80°) identical with that of an authentic sample.[29] The recovered aminoalcohols Ia and IIa (pyrolyses no. 2–5) as well as *cis*-N,N-dimethyl-2-methoxycyclohexylamine (Va, from pyrolysis no. 4) were identified by undepressed melting points of mixtures of their picrates with those of authentic samples. The oxazolidines IIIa (pyrolysis no. 2) and IVa (pyrolysis no. 5) were identified by comparison of their infrared spectra with those of authentic samples of *trans*- and *cis*-hexahydro-N-methylbenzoxazoline,[30] respectively. Both partially hydrolyzed during their isolation, giving *trans*- and *cis*-N-methyl-2-aminocyclohexanol, respectively. The former was identified by preparation of its phenylthiourea,[23] the latter by its N-benzoyl derivative.[31] None of these secondary aminoalcohols were present in the crude products (before acid treatment).

(B) **Products Obtained from the Aminocycloöctanols Ib and IIb.**—Gas chromatographic analyses and isolations of the individual compounds were carried out using column B[16] (at 130–160°) for the neutral fractions and column A[16] (at 160–180°) for the basic fractions. The compositions of the crude product mixtures in all cases remained unchanged throughout the isolation procedure. All products were identified by comparison of their infrared spectra with those of authentic samples. The syntheses of cycloöctanone,[22] *cis*-cycloöctene oxide[22] and 2-cycloöcten-1-ol[32] have been described previously; all other products from pyrolyses no. 7–9 were synthesized by unambiguous methods (see below).

***cis*-N,N-Dimethyl-2-methoxycyclohexylamine (Va).**—A mixture of 1 g. of *cis*-N,N-dimethyl-2-aminocyclohexanol hydrochloride and 0.3 g. of sodium hydride in 50 ml. of dry toluene was heated under reflux for 3 hr. A solution of 2.8 g. of dimethyl sulfate[33] in 10 ml. of toluene was added and the mixture was stirred and heated under reflux for 12 hr. Unreacted dimethyl sulfate was destroyed by stirring the cooled mixture with 12 ml. of 15% sodium hydroxide solution for 4 hr. The mixture was acidified with hydrochloric acid and evaporated under reduced pressure. The residue was dried over potassium hydroxide pellets and added to a solution of 2.6 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. After stirring and heating under reflux for 60 hr., the excess hydride was decomposed by successive addition of 2.6 ml. of water, 2.6 ml. of 15% sodium hydroxide solution and 7.8 ml. of water. Ether (60 ml.) was added and the mixture was heated under reflux for 1 hr. The precipitate was removed by filtration and washed well with ether. The combined filtrate and washings were extracted with three 10-ml. portions of 10% hydrochloric acid, the combined extracts were washed with 25 ml. of ether, and the acidic layer was concentrated to a sirup under reduced pressure. The residue was taken up in water and potassium hydroxide was added with cooling. The liberated amine was taken up in ether and the aqueous phase was extracted with three 25-ml. portions of ether. The combined ether extracts were dried over potassium hydroxide pellets and the ether was removed. Distillation of the residue through a semi-micro column gave 0.52 g. of a liquid, b.p. 85–90°(26 mm.). Gas chromatography (column A,[16] 160°) showed this material to contain 86% (0.45 g., 51% yield) of *cis*-N,N-dimethyl-2-methoxycyclohexylamine, 4% of starting material and 10% of an unidentified lower boiling material. The pure methoxyamine was isolated by gas chromatography. Its picrate melted at 147–149° (lit.[34] m.p. 140°).

***cis*-N,N-Dimethyl-2-methoxycycloöctylamine (Vb)** was prepared from *cis*-N,N-dimethyl-2-aminocycloöctanol as described above for the synthesis of Va. The methoxyamine was obtained in 29% yield, b.p. 77–78° (2 mm.), n^{25}D 1.4692.

Anal. Calcd. for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.21; H, 12.65; N, 7.38.

The picrate, after two crystallizations from methanol, melted at 123–124°.

Anal. Calcd. for $C_{17}H_{26}N_4O_8$: C, 49.27; H, 6.32; N, 13.52. Found: C, 48.95; H, 6.45; N, 13.30.

3-Methoxycycloöctene.—To a solution of sodium methoxide prepared from 1.05 g. of sodium and 20 ml. of absolute methanol was added 9.1 g. of 3-bromocycloöctene[35] in 15 ml. of methanol, and the mixture was stirred at room temperature for 8 days. It was poured into 100 ml. of ice-water and extracted with five 25-ml. portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, the solvent was removed, and the residue was distilled through a semi-micro column, yielding 3.8 g. (53%) of 3-methoxycycloöctene, b.p. 81–82° (22 mm.), n^{25}D 1.4677.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.96; H, 11.52.

Ethyl 2-Ketocycloöctanecarboxylate.—A solution of sodium ethoxide prepared from 18.3 g. of sodium and 400 ml. of absolute ethanol was cooled to 0° and an ice-cold solution of 100 g. of cycloöctanone[22] in 116 g. of diethyl oxalate was added to it. The mixture was stirred for 1 hr. at 0° and at room temperature for 5 additional hours. It was cooled to 0° and carefully neutralized by pouring onto a mixture of 22 ml. of concentrated sulfuric acid and 174 g. of cracked ice. The neutral mixture was diluted with water to a total volume of 2 l., the organic layer was separated, and the aqueous phase was extracted with three 250-ml. portions of benzene. The extracts were combined with the organic layer and the solvent was removed by distillation, first at atmospheric pressure and then at 40 mm. The residue was distilled under reduced pressure in a short-path still at a bath temperature of 170°, when a spontaneous loss of carbon monoxide occurred. The yield of ethyl 2-ketocycloöctanecarboxylate, after redistillation through a 30-cm. Vigreux column, was 49.5 g. (32%), b.p. 103–104° (4 mm.), n^{25}D 1.4861.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.68; H, 9.43.

Ethyl 1-Methyl-2-ketoxycycloöctanecarboxylate.—To a solution of sodium methoxide prepared from 5.4 g. of sodium and 200 ml. of absolute ethanol was added 46.5 g. of ethyl 2-ketocycloöctanecarboxylate. To the resulting white precipitate 100 g. of methyl iodide was added and the mixture was heated under reflux for 3.5 hr. Most of the low-boiling components of the mixture were removed by distillation, the mixture was cooled, 500 ml. of ice-water was added, and the mixture was extracted with three 250-ml. portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, the solvent was removed, and the residue was distilled through a 30-cm. Vigreux column yielding 45.3 g. (91%) of ethyl 1-methyl-2-ketocycloöctanecarboxylate, b.p. 73° (0.3 mm.), n^{25}D 1.4678.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 68.08; H, 9.57.

2-Methylcycloöctanone.—A mixture of 11.5 g. of potassium hydroxide in 100 ml. of methanol and 43.5 g. of ethyl 1-methyl-2-ketocycloöctanecarboxylate was heated under reflux for 18 hr. The mixture was cooled, the methanol was removed under reduced pressure, and the residue was taken up in 100 ml. of water, cooled in ice, and acidified with 30 ml. of concentrated hydrochloric acid. The mixture was extracted with three 50-ml. portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, the solvent was removed and the residue was distilled through a 100-cm. spinning band column, yielding 18.2 g. (64%) of 2-methylcycloöctanone, b.p. 86° (12 mm.), n^{25}D

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1.4656; its semicarbazone melted at 134–135° (lit.[36] b.p. 74–77° at 7 mm., n^{14}D 1.4675, m.p. of semicarbazone 127–128°).

Methylation of 2-methylcyclooöctanone was carried out according to Godchot and Cauquil.[36] A liquid, b.p. 123–124° (45 mm.), was obtained. Gas chromatographic analysis (column B,[16] 110°) showed it to be a mixture of four ketones, designated as A, B, C and D, present in the product mixture to the extent of 2, 40, 54 and 4%, respectively. Compound D was identified as unreacted starting material, ketone C was shown in another experiment to be 2,2-dimethylcyclooöctanone, while compounds A and B were not investigated further.

Separation of 2,2-dimethylcyclooöctanone from the ketone mixture was accomplished by the method of Bailey and Madoff.[37] To a suspension of methanol-free sodium methoxide prepared from 1.45 g. of sodium in 30 ml. of dry benzene was added an ice-cold mixture of 5.8 g. of ketones obtained in the preceding experiment (consisting of 4% of 2-methylcyclooöctanone and 96% of its higher homologs) and 4.7 g. of ethyl formate. The reaction vessel was evacuated, filled with nitrogen and allowed to stand at room temperature overnight. Ice-water (50 ml.) was added and the benzene phase was separated and extracted with three 25-ml. portions of 5% sodium hydroxide solution. The alkaline extracts were combined with the original aqueous phase, washed with ether, cooled in ice, and acidified with 10% hydrochloric acid. The resulting emulsion was extracted with two 50-ml. portions of ether, the solvent was removed, and the residue was dissolved in 300 ml. of 5% sodium hydroxide solution and distilled slowly through a 30-cm. Vigreux column. The distillate was saturated with sodium chloride and extracted with three 25-ml. portions of ether. The ethereal solution was dried over anhydrous magnesium sulfate, the ether was removed, and the residue was distilled through a semi-micro column, yielding a liquid, b.p. 70° (4 mm.) weighing 0.12 g. Analysis by gas chromatography (column B,[16] 110°) showed the presence of only one compound, the retention time of which was identical with that assigned to 2,2-dimethylcyclooöctanone in the original ketone mixture. Analysis of the benzene phase of the original reaction mixture by gas chromatography on the same column showed that the reaction leading to the formation of the hydroxymethylene derivative of the ketone proceeded to the extent of only *ca.* 10% under the above conditions.

***trans*-1,2-Hexamethylene-N-methyloxazolidine (IIIb)**.—To a solution of 5.6 g. of *trans*-N-methyl-2-aminocyclooöctanol[23] in 80 ml. of absolute ethanol were added 6.5 ml. of 37% aqueous formaldehyde solution and 6.5 g. of anhydrous potassium carbonate, and the mixture was stirred at room temperature for 48 hr. The potassium carbonate was removed by filtration and the filter cake was successively washed with two 45-ml. portions of benzene and two 70-ml. portions of ether. The filtrate and the washings were combined; to this mixture 6.5 g. of anhydrous potassium carbonate was added and stirring was continued for 24 hr. The mixture was filtered, the solvents were removed under reduced pressure, and the residue was distilled through a semi-micro column. The yield of *trans*-1,2-hexamethylene-N-methyloxazolidine was 5.4 g. (89%), b.p. 100–101° (6 mm.), n^{25}D 1.4786.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.66; H, 11.15; N, 8.37.

The picrate, after two crystallizations from methanol, melted at 173–175°.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.59; H, 5.66; N, 13.83.

***cis*-1,2-Hexamethylene-N-methyloxazolidine (IVb)**, b.p. 96–97° (6 mm.), n^{25}D 1.4824, was obtained in 77% yield from *cis*-N-methyl-2-aminocyclooöctanol[31] by the method described above for the synthesis of the *trans* isomer IIIb.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32. Found: C, 71.11; H, 11.34.

The picrate, after two crystallizations from methanol, melted at 168–170°.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.23; H, 5.58; N, 13.92.

Reaction of 2-Cyclohexen-1-ol with Tetramethylammonium Hydroxide.—A mixture of 0.3 g. of 2-cyclohexen-1-ol[27] and 1.1 g. of 45% aqueous tetramethylammonium hydroxide was heated in a sealed tube to 150° for 35 min. Water was added to the reaction mixture, which was then extracted with ether. The dried ether extracts were concentrated and analyzed by gas chromatography (column B,[16] 110°). The product contained unreacted 2-cyclohexen-1-ol and 3-methoxycyclohexene in a ratio of 2:1. No isomerization to cyclohexanone had occurred.

Reaction of Cyclohexanone with Tetramethylammonium Hydroxide.—A mixture of 0.2 g. of cyclohexanone and 0.9 g. of 45% aqueous tetramethylammonium hydroxide in a sealed tube was heated to 150° during 2.5 hr. The products were isolated as described above. Analysis by gas chromatography (column A,[16] 115°) showed the presence of 95% of unreacted cyclohexanone and 5% of 1-methoxycyclohexene.[29]

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Galvinoxyl (2,6-Di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadiene-1-ylidene)-*p*-tolyloxy)[1] as a Scavenger of Shorter-lived Free Radicals

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The long-lived free radical I ("galvinoxyl") reacts by coupling with both the 2-cyano-2-propyl radical and the *tert*-butoxy radical, the former radical becoming attached by its carbon and not its nitrogen to the scavenger molecule. Ready hydrolytic cleavage of both products to 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde is consistent with the structure VII for the coupling products. Galvinoxyl is a highly efficient scavenger for the free radicals produced from azobis-isobutyronitrile (yield about 66%) and from di-*tert*-butyl peroxyoxalate (yield >99%). The very small amount of geminate recombination within the solvent cage in the case of the latter initiator is discussed in relation to the activation energy for formation of an O–O bond, and to the separation of radicals within the cage by two carbon dioxide molecules. In competition experiments toward the 2-cyano-2-propyl radical, galvinoxyl is at least 10 times as reactive as molecular iodine.

Introduction

In studying the mechanisms of chain reactions there is frequent need to determine the rate at which reactive free radicals are produced. Such a measurement is often approximated by following the disappearance of a chain initiator which undergoes homolytic fission into a pair of free radicals. But there are several ways in which such measurements can fail to correspond to the true rate of chain

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[1] The 41-syllable designation in the outer set of parentheses is the official name of the stable free radical ("Chemical Abstracts Formula Index" 1957 and 1958). We are aware of a body of competent opinion deploring all trivial names and of a rising tide of acronymy (to be represented here perhaps by DBDBOCHDTO?). Believing that nomenclature, like the sabbath, was made for man and not *vice versa*, we use a euphonious nickname without apology.