Rearrangement of 1-Methyl-2-arylpyrrolidine N-Oxides to Tetrahydro-2-methyl-6-aryl-2H-1,2-oxazines

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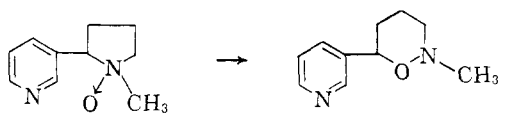
The behavior of some 1-methyl-2-substituted pyrrolidine oxides on pyrolysis was studied. With a 2-aryl substituent, rearrangement to tetrahydro-2-methyl-6-aryl-2H-1,2-oxazines occurred in good yield. With a 2-ethyl substituent, however, β-elimination rather than ring expansion occurred, and a product believed to be N-methyl-N-(4-hexenyl)hydroxylamine was formed. The methohydroxide of the 6-phenyl oxazine on pyrolysis afforded γ-dimethylaminobutyrophenone, thus confirming the orientation assigned to the ring (III rather than IV).

Rayburn, Harlan, and Hanmer[1] have reported the thermal rearrangement in high yield of nicotine oxide to tetrahydro-2-methyl-6-(3-pyridyl)-2H-1,2-oxazine.

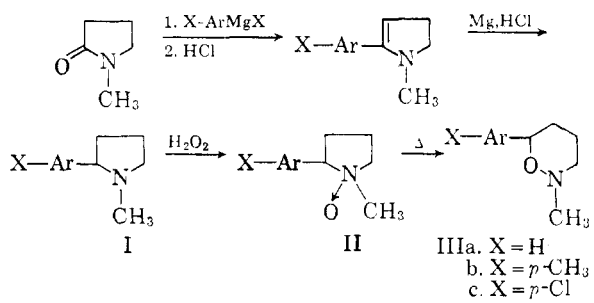


This reaction appears to be the only recorded example of pyrolysis of a pyrrolidine N-oxide. It is analogous to a rearrangement of amine oxides containing an allyl or benzyl substituent to O-allyl- or O-benzylhydroxylamines, discovered by Meisenheimer[2] and recently studied by Cope and Towle[3] and by Wragg, Stevens, and Ostle.[4] Different behavior is exhibited by amine oxides containing only alkyl groups, where attack by the oxide function on β-hydrogen occurs with formation of an olefin and a hydroxylamine.[5]

Very few tetrahydro-1,2-oxazines are known. We thought it likely that the rearrangement of 2-substituted pyrrolidine oxides might have more generality as a synthesis of these compounds than the isolated instance of Rayburn, *et al.*, might imply. In this paper, we report the successful use of this reaction for the preparation of three tetrahydro-2-methyl-6-aryl-2H-1,2-oxazines, a previously unknown group of compounds.

The starting materials for the synthesis are 1-methyl-2-arylpyrrolidines (I). These compounds were prepared easily, although in low yield (20–30%), from aryl Grignard reagents and N-methylpyrrolidone,[6] followed by reduction of the resulting pyrroline without its isolation.

The pyrrolidines dissolved slowly in excess 10% aqueous hydrogen peroxide, forming the soluble



N-oxides (II). These compounds were obtained as sirups on concentrating the solutions and were used in this form in the pyrolyses. They were analyzed as their picrates.

When heated in a bath to about 150–170° at 0.1–0.5 mm., a mobile liquid smoothly distilled from the N-oxides, leaving a black, tarry residue. Each of the three products so prepared gave two peaks on gas chromatography. The first peak, representing about 5–10% of the product, corresponded in retention time to the starting pyrrolidine,[7] while the major peak represented a new product. Fractional distillation provided the products in pure form. Analysis of the products and derivatives indicated structures isomeric with the pyrrolidine oxides. Infrared spectra showed no absorption for C=C or OH(of a hydroxylamine), which would be present if β-elimination had occurred. The products are therefore formulated as tetrahydro-1,2-oxazine derivatives (III). The oxazines also had strong absorption near 940 cm.$^{-1}$. This absorption disappeared on ring opening of a typical compound, IIIa (*vide infra*), and may be due to N—O stretching. Brown[8] attributes absorption at 927–971 cm.$^{-1}$ in oximes and oxime ethers, and at 870 cm.$^{-1}$ in N-alkylhydroxylamines, to N—O stretching. Cope mentioned an absorption band at 939 cm.$^{-1}$ for O-cycloöcten-3-yl-N,N-dimethylhydroxylamine[9] and at 943 cm.$^{-1}$ for an isoxazolidine, *cis*-N-methyl-3-oxa-2-azabicyclo-

(1) C. H. Rayburn, W. R. Harlan, and H. R. Hanmer, *J. Am. Chem. Soc.*, **72**, 1721 (1950). This result was recently confirmed by T. Kisaki, M. Ihida, and E. Tamaki, *Bull. Agr. Chem. Soc. Japan*, **24**, 719 (1960).

(2) J. Meisenheimer, *Ber.*, **52**, 1667 (1919); J. Meisenheimer, H. Greeske, and A. Willmersdorf, *ibid.*, **55**, 513 (1922).

(3) A. C. Cope and P. H. Towle, *J. Am. Chem. Soc.*, **71**, 3423 (1949).

(4) A. H. Wragg, T. S. Stevens, and D. M. Ostle, *J. Chem. Soc.*, 4057 (1958).

(5) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960).

(6) L. C. Craig, *J. Am. Chem. Soc.*, **55**, 295, 2543 (1933).

(7) Small amounts of the tertiary amine appear to be encountered commonly in pyrolyses of amine oxides.[5]

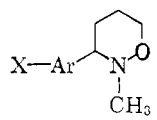
(8) J. F. Brown, *J. Am. Chem. Soc.*, **77**, 6341 (1955).

(9) A. C. Cope and C. L. Baumgardner, *ibid.*, **78**, 2812 (1958).

[3.3.0]octane.[10] Absorption due to $N^+—O^-$ of N-oxides has also been reported[11] at 943 cm.$^{-1}$.

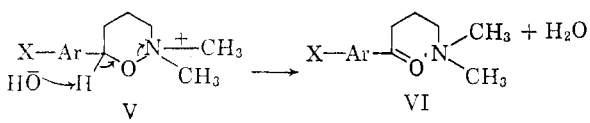
The yields of the three oxazines, based on the pyrrolidines, varied from 49% to 96%, and it appears that this reaction represents a useful means of obtaining these compounds. Those prepared in this work were easily isolated by distillation during their formation. Less volatile oxazines could presumably be extracted from the pyrolysis mixture. It may also be possible to effect the rearrangement in a solvent, as was done by Henry and Leete in a related rearrangement of gramine oxide.[12]

The oxazines formed in this rearrangement could conceivably have either structure III or IV.



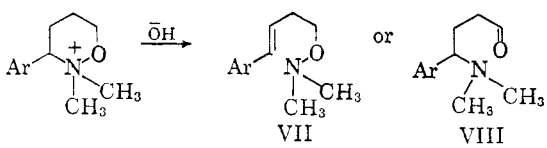
IV

The former would be favored as its formation would involve attack at a benzylic position by the N-oxide function. Rayburn, *et al.*,[1] proved their oxazine to be a 6-derivative (III) by hydrolytic as well as reductive ring cleavage to known pyridine derivatives, and we also sought confirmation in a cleavage reaction. The Hofmann degradation of the oxazine methohydroxides was considered for this purpose. It was reasoned that, if the original oxazine had structure III, attack by hydroxide on the oxazinium ion (V) would be at the benzylic position, with cleavage of the O—N bond to produce a ketone (VI).



V VI

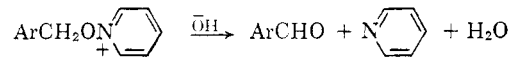
Different products (possibly VII or VIII) would result if structure IV were correct for the oxazine.



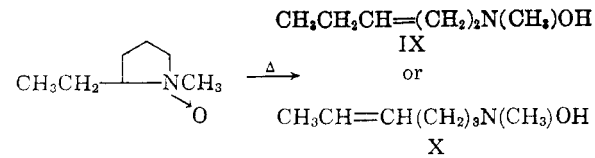
VII VIII

The methohydroxide of one of the oxazines, IIIa, prepared from the methiodide and moist silver oxide, was heated to a bath temperature of 200° at 0.3 mm. A volatile liquid distilled (41% yield). It formed a picrate and a 2,4-dinitrophenylhydrazone (obtained as the sulfate), both of which gave analyses consistent for derivatives of γ-dimethylaminobutyrophenone (VI. X=H). It formed a methiodide whose m.p. (233–235°) agreed with a published value (231–232°) for this compound.[13] The infrared spectrum of the base showed strong absorption at 1692 cm.$^{-1}$ for a conjugated aryl ketone.[14] No C=C absorption was noted. The ultraviolet spectrum showed maximum absorption in 95% ethanol at 241 mμ and weaker absorption at 279 mμ, as did acetophenone. All of these facts are consistent with structure VI for the Hofmann product, and this leaves no doubt that the oxazine originally possessed structure III.

The Hofmann degradation has apparently not previously been applied to cyclic hydroxylammonium hydroxides, but it is now evident that it constitutes a useful means of ring cleavage. A similar reaction has been observed in acyclic systems; Meisenheimer[15] reported the formation of aldehydes by heating O-alkyl-N,N,N-trimethylhydroxylammonium hydroxides. More recently, Feely, Lehn, and Boekelheide[16] described a synthesis of aromatic aldehydes based on the reaction of sodium hydroxide with quaternary salts of pyridine N-oxide.



It appears to be a requirement for the group migrating from N to O in Meisenheimer rearrangements of N-oxides to be of benzylic or allylic type.[17] It did not seem likely that 1-methyl-2-alkyl pyrrolidine oxides would give oxazines as had the 2-aryl derivatives. This was found to be the case by studying the pyrolysis of 1-methyl-2-ethylpyrrolidine oxide. A volatile product (45% yield) was obtained, which was analyzed as the hydrogen oxalate and found to be isomeric with the N-oxide. The infrared spectrum indicated the presence of a *trans* double bond[18] (maxima at 1675 and 965 cm.$^{-1}$) and an associated hydroxyl[19] (3200 cm.$^{-1}$, broad). Weak absorption noted at 858 cm.$^{-1}$ may be due to N—O stretching.[8] Structures IX and X, products of β-elimination, are therefore indicated.



IX or X

(10) A. C. Cope and N. LeBel, *J. Am. Chem. Soc.*, **82**, 4656 (1960).

(11) R. Mathis-Noël, R. Wolf, and F. Gallais, *Compt. rend.*, **242**, 1873 (1956).

(12) D. W. Henry and E. Leete, *J. Am. Chem. Soc.*, **79**, 5254 (1957).

(13) H. W. Bersch and G. Hübner, *Arch. Pharm.*, **291**, 88 (1958).

(14) L. L. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, N.Y., 1958, p. 137.

(15) J. Meisenheimer, *Ann.*, **397**, 273 (1913).

(16) W. Feely, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).

(17) A. C. Cope, E. Ceganek, and N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959), observed possible exceptions to this rule in the formation of small amounts of structures believed to be O-(5-norborn-2-enyl)-N,N-dimethylhydroxylamine and O-(2-norbornyl)-N,N-dimethylhydroxylamine from pyrolysis of the corresponding amine oxides.

(18) Ref. 14, chap. 3.

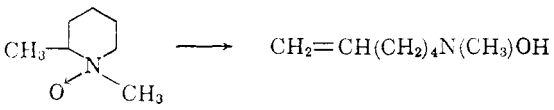
(19) Ref. 14, p. 95.

TABLE I

PROPERTIES OF NEW COMPOUNDS

Aryl	M.p. or b.p.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
A. 1-Methyl-2-arylpyrrolidine N-oxide picrates								
Phenyl	148–149.5 dec.	$C_{17}H_{18}N_4O_8$	50.24	49.97	4.47	4.51	13.79	13.54
p-Tolyl	178–182 dec.	$C_{18}H_{20}N_4O_8$	51.42	51.56	4.80	4.74	13.33	13.33
p-Chlorophenyl	186.5–188 dec.	$C_{17}H_{17}ClN_4O_8$	46.32	46.50	3.89	4.19	12.71	12.74
B. Tetrahydro-2-methyl-6-aryl-2H-1,2-oxazines								
Phenyl	93/0.30 mm.	$C_{11}H_{15}NO$	74.54	74.76	8.53	8.53	7.90	8.04
p-Tolyl	90–91/0.17 mm.	$C_{12}H_{17}NO$	75.35	75.55	8.96	8.72	7.32	7.53
p-Chlorophenyl	72/0.10 mm.	$C_{11}H_{14}ClNO$	62.41	62.50	6.67	6.51	6.62	6.70
C. Tetrahydro-2-methyl-6-aryl-2H-1,2-oxazine picrates								
Phenyl	158–159.5	$C_{17}H_{18}N_4O_8$	50.24	50.43	4.47	4.33	13.79	14.02
p-Tolyl	189–191	$C_{18}H_{20}N_4O_8$	51.42	51.27	4.80	4.75	13.33	13.37
p-Chlorophenyl	162–163	$C_{17}H_{17}ClN_4O_8$	46.32	46.48	3.89	4.11	12.71	12.45
D. Tetrahydro-2,2-dimethyl-6-aryl-2H-1,2-oxazinium iodides								
Phenyl	150–151.5	$C_{12}H_{18}INO$	45.15	45.04	5.69	5.51	4.39	4.52
p-Tolyl	145–146.5	$C_{13}H_{20}INO$	46.85	46.68	6.05	5.93	4.20	4.40
p-Chlorophenyl	150–151	$C_{12}H_{17}ClINO$	40.75	40.86	4.85	4.72	3.96	4.14

In pyrolysis of piperidine oxides, Cope and LeBel[10] found that a ring β-position did not participate in the elimination reaction; however, with an alkyl group in the 2-position offering alternative β-hydrogen, olefin formation occurred.



The requirement for a planar, five-membered cyclic transition state, attainable in the piperidine system only with involvement of the 2-alkyl group, was suggested as the explanation for this behavior. By analogy, therefore, the structure favored for the pyrrolidine oxide pyrolysis product would be X, as the steric situation is quite similar in the two ring systems. No further confirmation of structure X was obtained, however, since our interest rested primarily in determining if oxazine formation would occur.

Experimental

General.—Analyses were performed by Dr. Ing. A. Schoeller, Kronach, West Germany. Melting and boiling points are uncorrected. Infrared spectra were taken with a Perkin–Elmer Model 21 spectrophotometer. Ultraviolet spectra were obtained with a Cary Model 14 spectrophotometer. Gas chromatograms were obtained with a Perkin–Elmer Model 154-B Vapor Fractometer, using a 1-m. by 6-mm. column of polypropylene glycol 1025 on firebrick (30–60 mesh), 1:4.

1-Methyl-2-arylpyrrolidines.—The procedure of Craig[6] was used. The aryl Grignard reagent (from 1.0 mole of aryl bromide) in 600–800 ml. of ether was treated with 1.0 mole of N-methylpyrrolidone in 250 ml. of ether. The mixture was refluxed for 10–12 hr. and then treated with a mixture of ice and 200 ml. of concd. hydrochloric acid. The aqueous layer was then separated and treated slowly with magnesium turnings (1.0 g.-atom) while stirred vigorously. At the conclusion of the reaction, additional hydrochloric acid was added to dissolve any unchanged magnesium. The mixture was made strongly basic with concentrated sodium hydroxide and then steam distilled. The distillate was saturated with sodium sulfate, extracted with ether, and the extact dried with anhydrous sodium sulfate. The liquid remaining after removal of the ether was indicated by gas chromatography to contain impurities boiling higher than the pyrrolidine, and it was subjected to fractional distillation with a 2.4 by 40 cm. column of Heli-pak. The major fraction in each case then showed only one gas chromatographic peak.

1-Methyl-2-phenylpyrrolidine was obtained in 30% yield, b.p. 110° at 21 mm. (lit.,[6] 106° at 20 mm.), picrate m.p. 148–149° (lit.,[6] 146°). 1-Methyl-2-(*p*-chlorophenyl)pyrrolidine, 18% yield, had b.p. 73° at 0.42 mm. (lit.,[6] 118° at 9 mm.), picrate m.p. 180–181° (lit.,[6] 173°). Previously unreported 1-methyl-2-(*p*-tolyl)pyrrolidine, 19% yield, had b.p. 122° at 18 mm. It was analyzed as the picrate, m.p. 153–154°.

Calcd. for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.86. Found: C, 53.50; H, 4.86; N, 14.04.

1-Methyl-2-arylpyrrolidine Oxides.—The pyrrolidine (0.05 mole) was placed in 40 ml. of 10% hydrogen peroxide and the mixture stirred at room temperature. After several days, a clear solution resulted. A piece of platinum foil was added, and stirring continued for 1–2 days. The solution was then extracted with benzene, which removed some colored impurities and unreacted pyrrolidine. The aqueous solution was concentrated *in vacuo* to a viscous residue. This was used directly in pyrolysis experiments.

Small samples of each oxide were converted to the picrates, readily crystallized from absolute ethanol. M.p. and analytical data appear in Table I, Part A.

Rearrangement of Pyrrolidine Oxides to Tetrahydro-1,2-oxazines.—About 5–10 g. of the pyrrolidine oxide was placed in a 100-ml. flask attached to a trap in an ice bath followed by a trap in a Dry Ice bath. The system was evacuated to about 0.1–0.5 mm., and the flask slowly heated with an oil bath. Residual water was initially released by the oxide, and some crystallization occasionally occurred. At bath temperatures of about 120–150°, a dark melt was obtained, and smooth distillation of the oxazine commenced. A black residue remained; the distillate was generally straw-colored. The distillates from each of the three preparations were found by gas chromatography to contain 5–10% of the lower boiling pyrrolidine. The distillate from 1-methyl-2-(*p*-chlorophenyl)pyrrolidine oxide was shown to contain also about the same amount of an impurity boiling higher than the oxazine. Yields of the

three crude tetrahydro-2-methyl-6-aryl-2H-1,2-oxazines, based on the starting pyrrolidine, were: 6-phenyl, 96%; 6-*p*-tolyl, 49%; 6-*p*-chlorophenyl, 80%.

The crude products were fractionated *in vacuo* with a 1.0 cm. by 15-cm. column of Heli-pak. The major fraction showed a single gas chromatographic peak, and was analytically pure. B.p. and analytical data are recorded in Table I, Part B. The oxazines, initially colorless, turned slightly yellow on storage.

Picrates and methiodides were prepared in the conventional manner and were readily crystallized from aqueous or absolute ethanol. M.p. and analytical data are given in Table I, Parts C and D. Infrared spectra of the oxazines were taken on liquid films on salt plates. There was no absorption in the 1620–1680-cm.$^{-1}$ region for C=C, nor in the 3200–3400-cm.$^{-1}$ region for hydroxyl. The three oxazines had strong absorption bands in the N—O stretching region, as follows: 6-phenyl, 944 cm.$^{-1}$; 6-p-tolyl, 943 cm.$^{-1}$; 6-*p*-chlorophenyl, 940 cm.$^{-1}$.

Degradation of Tetrahydro-2,2-dimethyl-6-phenyl-2H-1,2-oxazinium Hydroxide.—To a solution of 2.9 g. of tetrahydro-2,2-dimethyl-6-phenyl-2H-1,2-oxazinium iodide in 35 ml. of water was added 4.0 g. of freshly prepared silver oxide. The mixture was stirred for 1.5 hr., during which time formation of a silver mirror occurred. The mixture was filtered, and the filtrate concentrated, leaving a viscous sirup containing some solid particles. The entire mass was heated *in vacuo*; at about 120° (bath temperature) and 0.3 mm., distillation commenced and continued slowly while the bath was raised to 200°. The distillation temperature remained at 105–108° at 0.1 mm.; the yield of liquid, which deposited some crystals on standing, was 0.74 g. (41%). Gas chromatography indicated the liquid to contain a trace of a higher boiling impurity. Further purification was not attempted.

The ultraviolet absorption spectrum (95% ethanol) showed λ_{max} 241 mμ (strong) and 279 mμ (weak). Identical λ_{max} were obtained for acetophenone. The infrared spectrum (liquid film on salt plates) had a strong absorption band at 1692 cm.$^{-1}$, indicative of a conjugated ketone; no absorption at 1620–1680 cm.$^{-1}$ was noted. The picrate, crystallized from absolute ethanol, had m.p. 126–128°.

Anal. Calcd. for $C_{18}H_{20}N_4O_8$: N, 13.33. Found: N, 13.34. An attempt to prepare the 2,4-dinitrophenylhydrazone[20] gave a brick-red precipitate, m.p. 213–214.5° (recrystallized from an aqueous ethanol–ethyl acetate mixture) which was indicated by analysis to be the sulfate of this derivative.

Anal. Calcd. for $C_{18}H_{21}N_5O_4 \cdot H_2SO_4$; N, 14.92. Found: N, 14.84. The methiodide, recrystallized from ethanol, had m.p. 233–235° (lit.,[13] m.p. 231–232°).

Preparation and Rearrangement of 1-Methyl-2-ethylpyrrolidine Oxide.—The reaction of ethylmagnesium bromide (1.75 moles) with N-methylpyrrolidone (1.25 moles) afforded, after hydrolysis, 1-methyl-2-ethyl-2-pyrroline.[6] Magnesium and acid failed to reduce it to the pyrrolidine, as reported[6]; the pyrroline was then recovered as its hydrochloride, and its reduction accomplished by refluxing for 3 days in a formic acid–potassium formate mixture[21] (prepared from 836 ml. of 98% formic acid and 168 g. of potassium hydroxide). The volume of the mixture was reduced to one-half by distillation, adjusted to pH 10 with sodium hydroxide, and steam distilled. The distillate was saturated with sodium sulfate and extracted with ether. After drying over potassium hydroxide, the extract was fractionally distilled, giving 22 g. (16% from N-methylpyrrolidone; some loss attended the unsuccessful magnesium reduction) of 1-methyl-2-ethylpyrrolidine, b.p. 123–124° (lit.,[6] b.p. 123°).

Twenty grams of the pyrrolidine was stirred for 2 days in excess 10% hydrogen peroxide; the mixture on being worked up as had the 2-aryl derivatives gave the N-oxide as a sirup. The picrate, after several recrystallizations from ethanol, had m.p. 173–178°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06. Found: C, 43.73; H, 5.12.

The N-oxide was heated slowly at 0.3–0.5 mm. Partial crystallization first occurred, followed by melting and then distillation at a bath temperature of 110–120°. The distillate (10.2 g., 45%) on fractionation gave 7.0 g., b.p. 47–48° at 0.40 mm. A picrate could not be obtained, but a hydrogen oxalate formed readily, m.p. 124–126°.

Anal. Calcd. for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.22; H, 7.47; N, 6.68.

Spectral properties suggested the distilled product to be either N-3-hexenyl- or N-4-hexenyl-N-methylhydroxylamine; indicative absorption bands were noted at 1675 cm.$^{-1}$ (nonterminal double bond), 964 cm.$^{-1}$ (*trans* double bond), 3200 cm.$^{-1}$ (associated hydroxyl), and 858 cm.$^{-1}$ (weak; possibly N—O stretching in NOH). No absorption near 940 cm.$^{-1}$ was noted.

Acknowledgment.—Appreciation is expressed to the American Tobacco Company for financial support of some of this work.

(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds" 4th ed., John Wiley & Sons, Inc., New York, N.Y., 1956, p. 219.

(21) R. Lukeš and V. Dědek, *Chem. Listy*, **51**, 2082 (1957).