A Chlorinative Ring Expansion. The Reaction of *t*-Butyl Hypochlorite and 1-Vinylcycloalkanols[1]

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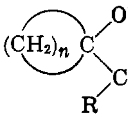
The reaction of 1-isopropenylcycloalkanols (**4**, **5**, and **6**) with *t*-butyl hypochlorite produces the ring-enlarged 2-chloromethyl-2-methylcycloalkanones (**7a**, **8**, and **9**). As in the related Tiffeneau–Demjanov reaction, decreasing yield with increasing ring size was observed. The conversion of 1-vinylcyclopentanol to 2-chloromethylcyclohexanone was found to occur in good yield. The use of other reagents and conditions for initiating the ring expansion reaction is discussed.

The homologation of alicyclic systems has been effected by a variety of cationic methods[3]; most notable are the Demjanov[4a,c] and Tiffeneau–Demjanov[4b,c] reactions, the acid-catalyzed dehydration of alcohols,[3] reactions with diazo compounds,[3,5] the solvolysis of sulfonates,[6] and the anodic oxidation of β-hydroxy acids.[7] In all these systems, one point of similarity is immediately obvious; all involve the generation of carbonium ion character on a carbon atom attached directly to the ring. Ring enlargement then generally occurs only when a new carbonium ion of lower energy is produced. Whether these changes occur stepwise through discrete carbonium ions, or whether through concerted processes, is not known.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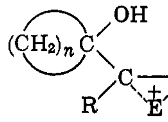
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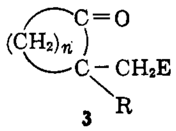
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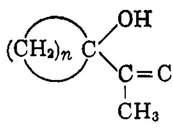
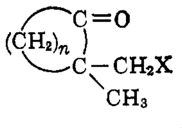
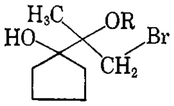
The addition of electrophiles to olefins is known to proceed through intermediates with significant cationic character. It was believed that suitably constructed olefinic alcohols (**1**) would undergo ring enlargement to **3** *via* the intermediate **2**, on treatment with an appropriate electrophile E^+. With this in mind, the simple allylic alcohols (**4**, **5**, and **6**) were prepared by the Grignard method.[8]

The majority of the experiments for optimization of conditions were performed on the five-membered ring (**4**).


4, $n = 4$
5, $n = 5$
6, $n = 6$


7a, $n = 4$; X = Cl
7b, $n = 4$; X = Br
8, $n = 5$; X = Cl
9, $n = 6$; X = Cl

Treatment of **4** with bromine in carbon tetrachloride at −2° produced a complex mixture whose infrared exhibited only weak absorption in the carbonyl region. It was thought a more polar solvent might facilitate the ionic rearrangement. The use of ether as a solvent produced only minor improvements. When water was employed as a solvent, however, the vapor phase chromatogram of the crude product indicated the presence of one major component in *ca.* 80–90% yield. The infrared spectrum of a portion of the main component collected from the column indicated that it was a six-membered ketone (1715 cm.$^{-1}$). The infrared spectrum of the crude material exhibited only a weak carbonyl band at 1715 but a strong hydroxyl peak at 3550 cm.$^{-1}$. Evidently the elements of HOBr had added to **4** producing the bromo diol **10** (R = H), which dehydrates (presumably in the injection port since the peak which elutes is quite symmetrical) to produce the desired ketone **7b**.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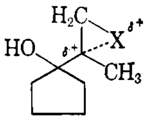
11a, X = Br
b, X = Cl

Despite the lower nucleophilicity of acetic acid, its use as a solvent in bromination led to a crude material whose infrared spectrum exhibited two carbonyl peaks (1705 and 1715 cm.$^{-1}$) along with a C–O stretching vibration (1245 cm.$^{-1}$). A mixture of ketone **7b** and a bromo hydroxy acetate (**10**, R = CH_3CO–) is compatible with this spectrum. Addition of sodium acetate to the aqueous reaction mixture might be expected to reduce side reactions by buffering of the acid formed. This expectation was not realized and results were similar to reactions wherein acetic acid was used as a solvent. Subsequent treatments of the crude products from aqueous brominations [presumed to be predominately **10** (R = H)] with acids (acetic or sulfuric) under a variety of conditions were also unrewarding. Variation of the temperature of the reaction produced no appreciable improvement.

During the course of this investigation a recent report of related work by Julia, *et al.*,[9] was noted. In their investigation, these workers reported the conversion of the alcohol **4** to the ketone **7b** by treatment with N-bromosuccinimide in a mixture of aqueous perchloric acid and dioxane. The ketone **7b**, prepared in unspecified yield in this manner without purification, was reported

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[1] Presented before the Organic Division at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug., 1964.

[2] From the Ph.D. Thesis of C. J. C., Jan., 1964.

[3] R. A. Raphael, "The Chemistry of Carbon Compounds," Vol. IIA, E. N. Rodd, Ed., Elsevier Press Inc., New York, N. Y., 1953, p. 11.

[4] (a) N. J. Demjanov and M. Luschnikov, *J. Russ. Phys. Chem. Soc.*, **33**, 279 (1901); (b) M. Tiffeneau, P. Weill, and B. Tchoubar, *Compt. rend.*, **205**, 54 (1937); (c) P. A. S. Smith and D. R. Baer, *Org. Reactions*, **11**, 157 (1960).

[5] L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1962, p. 451.

[6] E. J. Corey, M. Ohno, P. A. Vatakencherry, and R. B. Mitra, *J. Am. Chem. Soc.*, **83**, 1251 (1961).

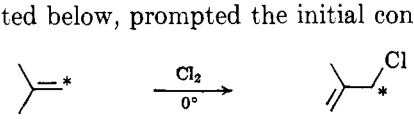
[7] E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanova, Jr., and E. T. Kaiser, *ibid.*, **82**, 2645 (1960).

[8] H. Normant, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 1.

[9] S. Julia, M. Julia, H. Linarès, and J.-C. Blondel, *Bull. soc. chim. France*, 1952 (1962).

to decompose above 40°. Satisfactory analysis was obtained for the semicarbazone. It has been observed in the present work that the crude reaction mixture obtained by treatment of **4** with aqueous solutions of bromine did indeed color deeply in standing, even at room temperature; heating on a steam bath produced a rapid deep purple coloration. These changes occurred with almost no change in the infrared spectrum, however. The ketone **7b** could also be collected as a colorless oil from a vapor phase chromatography column at 210°. The coloration then appeared to be due not to decomposition of **7b** but to some contaminant. Because of difficulties encountered in this work, and apparently in that of Julia, it was decided to investigate the possible use of chlorine as a cationic initiator in this rearrangement.

The chlorination of isobutylene to produce methallyl chloride,[10] and the elucidation of the ionic nature and mechanism of the reaction by radioactive tracer studies,[11] as illustrated below, prompted the initial consideration



of the use of chlorine in the ring enlargement of **4**. Treatment of the alcohol **4** with chlorine in chloroform indeed yielded a larger amount of ketonic material than similar treatment with bromine, but the reaction mixture was contaminated with nearly a dozen other products, presumably arising from radical processes.

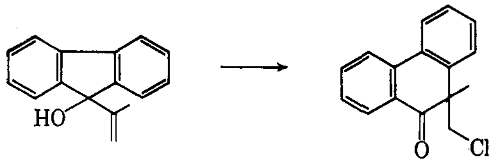
Stabilization of the carbonium ion on the exocyclic carbon atom retards ring enlargement in the Demjanov and Tiffeneau–Demjanov rearrangements.[3c] The fact that chlorine promotes ring enlargement to a greater extent than bromine is perhaps a reflection of the increased stability of the carbonium ion **11a** compared to that of **11b**. While the replacement of bromine by chlorine furnished promising results, they were far from satisfactory. The rearrangement was attended by the formation of numerous products of competitive reactions which rendered separation and purification of the ketone difficult.

The use of *t*-butyl hypochlorite[12] as a mild chlorination agent has been reviewed.[13] Should this reagent be capable of initiating the desired rearrangement, there would be the obvious advantages gained by the formation of neutral *t*-butyl alcohol as byproduct, rather than acid as in the case of chlorine. The reaction of the alcohol **4** with *t*-butyl hypochlorite in aqueous solution was very rapid and produced an oil, which on the basis of the infrared spectrum was presumed to be a mixture of the diol **10** (R = H) and the desired chloro ketone **7a**. The same reaction in chloroform[14] was quite slow at room temperature, and even after several hours appreciable amounts of starting alcohol remained. Refluxing, while it increased the rate of the reaction, produced a variety of products reminiscent of the reaction of **4** with chlorine in chloroform. In chloroform at 50–55° in the dark, however, the alcohol **4** rearranged cleanly, and in almost quantitative yield, to the desired ketone **7a**. The crude ketone, obtained by evaporation of the solvent *in vacuo*, afforded a crystalline semicarbazone in 68% yield. The ketone could be regenerated from the semicarbazone in 93% yield, and was obtained pure after one distillation.

Similar ring enlargements of the higher homologs **5** and **6** to the corresponding ketones **8** and **9**, respectively, were realized, but, like the Tiffeneau–Demjanov rearrangement, decreasing yield with increasing ring size was found to be the case.[15]

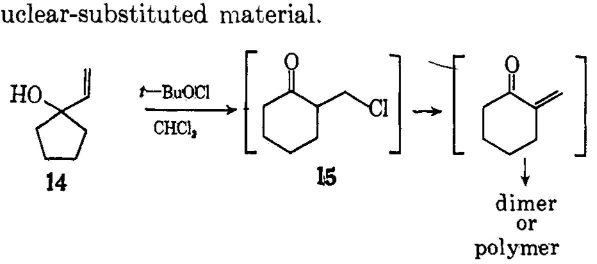
Treatment of the alcohol **5** with *t*-butyl hypochlorite in chloroform produced two compounds in the ratio of *ca.* 1:1. The compounds were separated by fractional distillation and the more volatile material was shown to be the desired ketone **8** obtained in 38% yield, while the higher boiling material remains unidentified. The yield of the ketone **9**, produced by treatment of the alcohol **6** with *t*-butyl hypochlorite in chloroform, was 34%.

It seemed desirable to subject the alcohol **12** to the ring-expansion conditions for several reasons. The alcohol **12** and its rearrangement product **13** were anticipated to be solid and thus easily purified by crystallization and readily characterized. In addition, the product **13** was expected to be an interesting example of a cyclohexadienone of the phenanthrene series. The alcohol **12** proved to be a viscous oil, which was obtained pure only by chromatography, low temperature crystallization, and short-path distillation. The pure alcohol **12** was colorless oil, which on standing turned a pale yellow-green possibly owing to anionotropic rearrangement.



12 **13**

Treatment of **12** with *t*-butyl hypochlorite produced a crystalline solid in good yield, whose infrared and n.m.r. spectra were in accord with the proposed structure **13**. The infrared spectrum of **13** exhibited a carbonyl band at 1680 cm.$^{-1}$, and the n.m.r. spectrum showed a three-proton singlet at 1.76 CCH_3, a two-proton pair of unsymmetrical doublets at 4.58 CCH_2Cl, and an eight-proton complex aromatic multiplet centered at 8.80 p.p.m. The ketone **13** continually gave high chlorine analytical values, possibly due to a small amount of nuclear-substituted material.



14 **15**

Preliminary experiments on the chlorinative ring enlargement of 1-vinylcyclopentanol (**14**), prepared by the action of vinylmagnesium chloride on cyclopentanone, have indicated that rearrangement to the corresponding 2-chloromethylcyclohexanone (**15**) proceeds

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[10] J. Burgin, W. Engs, H. P. A. Groll, and G. Hearne, *Ind. Eng. Chem.*, **31**, 1413 (1939).

[11] W. Reeve and D. H. Chambers, *J. Am. Chem. Soc.*, **73**, 4499 (1951).

[12] H. M. Teeter and E. W. Bell, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 125.

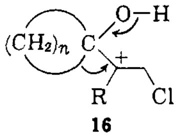
[13] M. Anbar and D. Ginsberg, *Chem. Rev.*, **54**, 925 (1954).

[14] An attempt was made to run this rearrangement employing tetrahydrofuran as solvent. Tetrahydrofuran and *t*-butyl hypochlorite react *vigorously* even in the dark.

[15] B. Tchoubar, *Bull. soc. chim. France*, 164 (1949).

easily. The product, however, was unstable and lost the elements of hydrochloric acid on standing at room temperature. The crude reaction mixture could be catalytically reduced over a palladium catalyst in the presence of sodium acetate to produce 2-methylcyclohexanone, identified by vapor phase chromatographic comparison with an authentic sample, and by melting point and mixture melting point of the semicarbazone.

It is interesting to speculate on the possible mechanism of this chlorinative ring enlargement of 1-isopropenylcycloalkanols with *t*-butyl hypochlorite. It may be assumed on the basis of the chlorination of olefins that *t*-butyl hypochlorite is a source of positive halogen. Chlorination may occur first to produce intermediate **16**, followed by rearrangement and proton loss to the chloro ketone. Alternately, the process may be visualized as a concerted chlorinative rearrangement, as depicted below (**17**).



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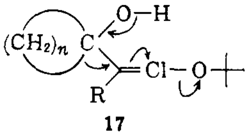

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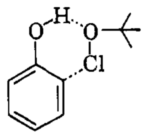
Ginsberg[16] has shown that chlorination of phenol with *t*-butyl hypochlorite produces the *ortho* isomer in good yield. Chlorination of phenol with chlorine, however, produces predominantly the *para* isomer. It might be argued on these grounds that the six-membered cyclic state **18** is involved. In like manner, a hydrogen-bonded complex (**19**) may intervene during the chlorinative ring expansion.

A pathway involving hypochlorite exchange, followed by an intramolecular rearrangement (**20**), appears less likely.



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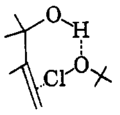

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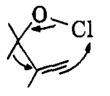

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Work now in progress is designed to provide additional information as to the mechanism of this rearrangement, the scope of the reaction with respect to substituent effects and electrophile, and the reactions of the 2-chloromethyl cycloalkanones.

Experimental

1-Isopropenylcyclopentanol (4).—To a cold solution of the Grignard reagent, prepared from 15.1 g. (0.125 mole) of 2-bromopropene and 3.2 g. (0.13 g.-atom) of magnesium in 75 ml. of tetrahydrofuran, was added dropwise with stirring 8.4 g. (0.1 mole) of cyclopentanone in 40 ml. of dry tetrahydrofuran. The mixture was stirred at 40° overnight and then cooled; the salt was decomposed by the dropwise addition of a cold, saturated solution of ammonium chloride. The mixture was filtered and the precipitate was washed thoroughly with ether. The filtrate and ether washings were combined, washed with water, dried over sodium sulfate, and concentrated. The oil was distilled to provide 4.8 g. (38%) of 1-isopropenylcyclopentanol: b.p. 88–90° (36 mm.); $n^{25}\mathrm{D}$ 1.4735 [lit.[17] b.p. 76° (17 mm.); $n^{20}\mathrm{D}$ 1.4662]; $\nu_{\max}^{\text{neat}}$ 3400, 2930, 1645, 1183, 988, and 900 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.04; H, 11.36.

1-Isopropenylcyclohexanol (5).—The alcohol **5** was prepared in 38% yield by the same procedure as that described for the preparation of **4**. The pure material had b.p. 58–59° (4.0 mm.); $n^{26}\mathrm{D}$ 1.4800; $\nu_{\max}^{\text{neat}}$ 3400, 2910, 1648, 1445, 1177, 965, and 900 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.28; H, 11.54.

1-Isopropenylcycloheptanol (6).—The alcohol **6** also was prepared in 38% yield, as described above for alcohol **4**. It was obtained as a colorless oil: b.p. 63–64° (1.5 mm.); $n^{25}\mathrm{D}$ 1.4896; $\nu_{\max}^{\text{neat}}$ 3400, 2910, 1648, 1460, 1029, and 900 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.95; H, 11.65.

9-Isopropenylfluoren-9-ol (12).—The alcohol **12** was prepared in 38% yield by the usual Grignard procedure. It was obtained as a colorless oil after chromatography on alumina (hexane–benzene, 95:5), low temperature crystallization from hexane, and short-path distillation: b.p. 95–100° (0.05 mm.); $n^{25}\mathrm{D}$ 1.6234; $\nu_{\max}^{\text{neat}}$ 3650, 3450, 1650, 1450, 1055, 905, 770, 755, and 732 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.36; H, 6.45.

1-Vinylcyclopentanol (14).—Dry vinyl chloride was passed through a stirred refluxing mixture of 13.5 g. (*ca.* 0.55 g.-atom) of magnesium turnings in 300 ml. of dry tetrahydrofuran in a three-necked flask equipped with a Dry Ice–acetone condenser, until most of the magnesium had reacted (5–6 hr.). The mixture was cooled to room temperature, and 33.6 g. (0.4 mole) of cyclopentanone in 50 ml. of tetrahydrofuran was added over a 1-hr. period. The mixture was allowed to stir at room temperature overnight. It was then cooled in ice, and an ice-cold saturated, aqueous solution of ammonium chloride was added dropwise with stirring, until an amorphous precipitate separated. The mixture was filtered and the filter cake was washed thoroughly with fresh ether. The combined filtrate and ether washings were washed with water until neutral, dried, and concentrated to leave 43.7 g. of a yellow oil. The oil was distilled through a heated, jacketed 0.7 × 35 cm. Podbielniak column. The fraction boiling at 68–70° (26 mm.) was collected as 1-vinylcyclopentanol: $n^{25}\mathrm{D}$ 1.4697 [lit.[18] b.p. 68–70° (30 mm.); $n^{20}\mathrm{D}$ 1.4660]; $\nu_{\max}^{\text{neat}}$ 3390, 2975, 1648, 993, 982, and 917 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{12}O$: C, 75.00; H, 10.70. Found: C, 74.92; H, 10.90.

2-Chloromethyl-2-methylcyclohexanone (7a).—To a stirred solution of 126 mg. (1 mmole) of the alcohol **4** in 4 ml. of alcohol-free chloroform in a black-painted flask at 55°, was added 0.16 ml. (1.3 mmoles) of freshly distilled *t*-butyl hypochlorite, and the solution was allowed to stir for 12 hr. The mixture was concentrated *in vacuo* to leave 166 mg. of a colorless oil. Vapor phase chromatographic analysis on a Carbowax column at 190° showed the crude oil to consist almost entirely of one component. Traces of chloroform and a small amount (*ca.* 3–4%) of starting alcohol were present. The material afforded 152 mg. (68%) of a crystalline **semicarbazone**, m.p. 146–147° dec. from methanol.

Anal. Calcd. for $C_9H_{16}ClN_3O$: C, 49.65; H, 7.41; Cl, 16.29; N, 19.30. Found: C, 49.56; H, 7.48; Cl, 16.56; N, 19.46.

Steam distillation of 1.32 g. (0.00475 mole) of the semicarbazone from 1 *N* hydrochloric acid provided the ketone in 93% crude yield. The pure ketone **7a** was obtained as a colorless oil by short-path distillation: b.p. 58–59° (1.0 mm.); $n^{25.9}\mathrm{D}$ 1.4800; $\nu_{\max}^{\text{neat}}$ 2940, 1710, and 1450 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{13}ClO$: C, 59.81; H, 8.15; Cl, 22.07. Found: C, 60.08; H, 8.35; Cl, 22.12.

2-Chloromethyl-2-methylcycloheptanone (8).—To a stirred solution of 1.7 g. (1.2 mmoles) of the alcohol **5** in 55 ml. of alcohol-free chloroform, was added 2.0 ml. (1.5 mmoles) of freshly distilled *t*-butyl hypochlorite, and the solution was allowed to stir in the dark at 50° for 37 hr. The solution was then filtered through a short column (20 g.) of alumina and concentrated to leave 2.1 g. of a pale yellow oil. Distillation through a 0.7 × 7 cm. jacketed Vigreux column afforded 800 mg. (38%) of a colorless oil: b.p. 55–60° (1.8 mm.); $n^{25}\mathrm{D}$ 1.4863; $\nu_{\max}^{\text{neat}}$ 2950, 1700, and 1460 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{15}ClO$: C, 61.88; H, 8.66. Found: C, 61.86; H, 8.59.

2-Chloromethyl-2-methylcyclooctanone (9).—The ketone was prepared from the alcohol **6** by the same procedure described

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[16] D. Ginsberg, *J. Am. Chem. Soc.*, **73**, 2723 (1951).

[17] N. J. Demjanov and M. Luschnikov, *J. Russ. Phys. Chem. Soc.*, **35**, 26 (1903); *Chem. Zentr.*, **74**, 828 (1903).

[18] V. F. Kucherov and E. P. Serebryakov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1057 (1960); *Chem. Abstr.*, **55**, 475*h* (1961).

above for the ketone **8**. The ketone was obtained in 34% yield as a colorless oil: b.p. 70–74° (0.49 mm.); $n^{25.8}\text{D}$ 1.4882; $\nu_{\text{max}}^{\text{neat}}$ 2920, 1693 and 1462 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 63.60; H, 9.06.

10-Chloromethyl-10-methyl-9(10H)-phenanthrone (13).—To a stirred solution of 222 mg. (1 mmole) of the alcohol **12** in 4 ml. of alcohol-free chloroform, was added 0.16 ml. (1.3 mmoles) of freshly distilled *t*-butyl hypochlorite, and the solution was allowed to stir in the dark at 55° for 15 hr. Concentration of the solution afforded 275 mg. of an orange oil that solidified on standing. The material was recrystallized once from hexane (Norit) and then six times from aqueous ethanol. The ketone **13** was obtained as colorless crystals: m.p. 118–119°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 2990, 1660, 1603, 1480, 1443, 1290, 1265, and 980 cm.$^{-1}$; n.m.r. singlet at δ 1.76 (3H), pair of doublets centered at 4.58 (2H), and complex aromatic pattern centered at 8.80 (8H).

Anal. Calcd. for $C_{16}H_{13}ClO$: C, 74.85; H, 5.10; Cl, 13.82. Found: C, 72.83 and 72.84; H, 4.83 and 5.02; Cl, 15.87.

2-Methylcyclohexanone Semicarbazone.—To a solution of 2.24 g. (20 mmoles) of the alcohol **14** in 7 ml. of alcohol-free chloroform, was added 2.8 ml. (23 mmoles) of *t*-butyl hypochlorite and the solution was allowed to stir in the dark at 58–60° for 4 hr. Concentration of the mixture afforded 3.92 g. of a colorless oil whose infrared spectrum (neat) exhibited a strong carbonyl peak at 1713 cm.$^{-1}$. The vapor phase chromatogram of the crude material on Carbowax was found to vary with the sample size. Injection of a small amount (2 μl.) showed the mixture to contain only one major component. Injection of amounts exceeding 25 μl. caused the appearance of a new compound, which eluted before the major peak. A portion of the new substance was collected and examination of its infrared spectrum revealed the presence of a new carbonyl peak at 1670 cm.$^{-1}$. The new material was presumed to be 2-methylenecyclohexanone. The crude oil from the ring expansion was dissolved in a mixture of 15 ml. of absolute ethanol, 3 g. of sodium acetate, and 600 mg. of 10% palladium on carbon. The resulting mixture was hydrogenated at 55 p.s.i.g. for *ca.* 24 hr. at room temperature. The mixture was filtered through Celite and concentrated *in vacuo* to *ca.* 10 ml. To a small portion, water was added and the mixture was extracted with ether. The ether extracts were combined, washed with water, dried, and concentrated to leave a small amount of a colorless oil. Vapor phase chromatographic analysis of the oil indicated the presence of three new compounds in addition to the starting ketone **15**. The major compound eluted first, and was not separated from authentic 2-methylcyclohexanone on analysis of a synthetic mixture. Water was added to the remainder of the crude hydrogenation mixture until a faint cloudiness persisted and 6 g. each of semicarbazide hydrochloride and sodium acetate were added. The mixture was refluxed on a steam bath for 15 min. and cooled in ice; the precipitated semicarbazone was filtered. One crystallization from aqueous methanol afforded 1.46 g. of colorless crystals, m.p. 190–195°. The melting point was not depressed on admixture with an authentic sample.

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Synthesis of Oximes[1]

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Alkyl-substituted heteroaromatic compounds and allyl-substituted benzenes were oximinated in liquid ammonia at −33° with sodamide and an alkyl nitrite. Oximes were obtained from 2-, 3-, and 4-picoline, 2,4- and 2,6-lutidine (monooximes), 4-ethylpyridine (ketoxime), 2-methylquinoline, 2-methylpyrazine, 2-methylbenzoxazole, 2-methylbenzothiazole, allylbenzene, and indene. The effects of other metalation agents and other solvents were determined. The oximes were assigned configurations on the basis of n.m.r. evidence.

Pyridinecarboxaldehyde oximes can be quaternized with alkyl halides to form compounds which are known to be antidotes for "nerve gas" poisons[2] and it was therefore of interest to develop a direct route to these intermediates. One such synthesis would result from the oximination of picoline, but numerous attempts in

TABLE I

PREPARATION OF 2-PYRIDINECARBOXALDEHYDE OXIME[a]

Expt.	NH_3, ml.	2-picoline, moles	Bu ONO, moles[b]	Yield, %[c]
1	1500	2.0	1.0	56
2	1000	2.0	1.0	61
3	1000	2.0	1.2	53
4	1000	3.0	1.0	68[d]
5	670	2.0	1.0	66
6	535	2.0	1.0	64
7	535	3.0	1.0	74
8	470	3.0	1.0[e]	71
9[f]	400	3.0	1.0	75
10	400	4.0	1.0	74
11	270	3.0	1.0	47

[a] Effect of variations in the proportions of reagents with 2.0 g.-atoms of sodium in liquid anhydrous ammonia. [b] Diluted with an equal volume of ethyl ether. [c] Two g.-atoms of sodium required theoretically to produce 1 mole of oxime. [d] Yield of 73.5% based on 2-picoline consumed. [e] Diluted with 500 ml. of ethyl ether. [f] Preferred conditions. See Experimental.

TABLE II

PREPARATION OF 2-PYRIDINECARBOXALDEHYDE OXIME[a]

Expt.	Solvent	Metalation agent	Nitrite[b]	Yield, %[c]
1	NH_3[d]	$NaNH_2$[d]	n-C_4H_9ONO[d]	75
2	NH_3	$NaNH_2$	N_2O_3	0
3	NH_3	$NaNH_2$	CH_3ONO	34
4	NH_3	$NaNH_2$	$C_8H_{17}ONO$[e]	49
5	NH_3[f]	KNH_2[f]	n-C_4H_9ONO[f]	70
6	T.H.F.[g]	KNH_2	n-C_4H_9ONO	7
7	NH_3	$LiNH_2$	n-C_4H_9ONO	0
8	T.H.F.[g]	$LiNH_2$	n-C_4H_9ONO	0
9	Et_2O[h]	C_6H_5Li	n-C_4H_9ONO	0
10	Et_2O[i] + NH_3[i]	C_6H_5Li	n-C_4H_9ONO	1
11	T.H.F.[g]	C_2H_5MgBr	n-C_4H_9ONO	0

[a] Variations of the types of metalation agents and nitrite in runs of 0.1-mole quantities of each reactant with 50 ml. of solvent, except where noted. [b] Dissolved in 10 ml. of ethyl ether and added 1 hr. after addition of 2-picoline. [c] Two moles of metalation reagent required theoretically to produce 1 mole of oxime. [d] Method, quantities, and proportions for this run are the preferred conditions described in Experimental section. [e] 2-Ethylhexyl nitrite. [f] 500 ml. of NH_3, 1.0 mole of KNH_2, 0.6 mole of BuONO in 60 ml. of Et_2O, 1.0 mole of 2-picoline. [g] Tetrahydrofuran. Same solvent (10 ml.) used for the nitrite. [h] 100 ml. [i] 110 ml. of Et_2O; 150 ml. of liquid NH_3 added 1 hr. after addition of 2-picoline; butyl nitrite added 1 hr. after NH_3.

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[1] Presented at the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964.

[2] S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).