C=C stretching); $\delta_{TMS}^{CCl_4}$ 1.38 [singlet, 9 H, $C(CH_3)_3$], 5.79 (singlet, 1 H, OH), and *ca.* 7.0 (multiplet, 3 H, aromatic protons); lit.[31] bp 144–146° (26 mm).

2,4-Dichloro-6-*t*-butylphenol (20) was isolated as a pale yellow liquid: $\nu_{max}^{CCl_4}$ 3690 (OH stretching) and 1575 cm^{-1} (aromatic >C=C< stretching); $\delta_{TMS}^{CCl_4}$ 1.35 [singlet, 9 H, $C(CH_3)_3$], 5.80 (singlet, 1 H, OH), and 7.15 (singlet, 2 H, aromatic protons); lit.[32] bp 142° (22 mm).

2,6-Di-*t*-butyl-4-chlorophenol (21) was obtained as a white solid: mp 78–79° (lit.[33] mp 79.0–79.5°); $\nu_{max}^{CCl_4}$ 3775 (OH stretching) and 1575 cm^{-1} (aromatic >C=C< stretching); $\delta_{TMS}^{CDCl_3}$ 1.30 [singlet, 18 H, $C(CH_3)_3$], 5.01 (singlet, 1 H, OH), and 7.08 (singlet, 2 H, aromatic protons).

The residue from the above distillation was slurried in cold hexane and filtered to give 1.1 g (8%) of **10**, mp 245–246°.

Chlorination of 2,6-Di-*t*-butyl-4-methylphenol (6).—A 16-g (0.07 mole) sample of **6** was chlorinated with 10 g (0.14 mole) of chlorine as described above. Distillation of the reaction mixture afforded 5.3 g of a yellow crystalline distillate which was composed of 96% **6** and 4% **2-chloro-4-*t*-butyl-6-methylphenol (22)**. Preparative vpc of the latter component gave a pale yellow oil with the following spectral properties: $\nu_{max}^{CCl_4}$ 3700 (OH stretching) and 1575 cm^{-1} (aromatic >C=C< stretching); $\delta_{TMS}^{CCl_4}$ 1.50 [singlet, 9 H, $C(CH_3)_3$], 2.24 (singlet, 3 H, aryl CH_3), 5.65 (singlet, 1 H, OH), and 6.98 (singlet, 2 H, aromatic protons); lit.[34] bp 105–106° (10 mm).

The residue from the distillation was slurried in cold ethanol and filtered. After recrystallization of the residue from ethanol, there was obtained 3.8 g (26%) of **23** as a pale yellow solid: mp 186–188° (lit.[35] mp 187–189°); $\nu_{max}^{CCl_4}$ 3600 (OH stretching), 1690 (C=O stretching), and 1575 cm^{-1} (aromatic >C=C< stretching); $\delta_{TMS}^{CDCl_3}$ 1.50 [singlet, 18 H, $C(CH_3)_3$], 5.88 (singlet, 1 H, OH), 7.81 (singlet, 2 H, aromatic protons), and 9.96 (singlet, 1 H, aldehydic proton).

Registry No.—**7**, 2417-04-1; **8**, 13395-83-0; **9**, 3432-00-6; **10**, 2455-14-3; **11**, 6476-26-2; **12**, 809-73-4; **13**, 1516-94-5; **19**, 13395-85-2; **20**, 13395-86-3; **21**, 4096-72-4; **22**, 13395-07-8; **23**, 1620-98-0.

(31) G. Stork and W. N. White, *J. Am. Chem. Soc.*, **78**, 4604 (1956).
(32) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957).
(33) W. C. Sears and L. J. Kitchen, *J. Am. Chem. Soc.*, **71**, 4110 (1949).
(34) W. H. Starnes, Jr., *J. Org. Chem.*, **31**, 3164 (1966).
(35) G. R. Yoke, J. E. Dunbar, R. L. Pedrotti, F. M. Scheidt, R. G. H. Lee, and E. E. Smith, *ibid.*, **21**, 1289 (1956).

Oxocane. Synthesis and Conformational Isomerization[1]

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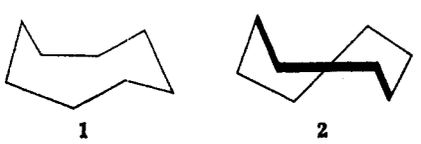
An unequivocal synthesis of oxocane, the cyclic eight-membered ring ether related to cyclooctane, is described. Low-temperature nmr analysis of the possible conformations and conformational processes available to this heterocyclic system suggested that the introduction of the oxygen atom served to facilitate ring-inversion processes, at least when compared to cyclooctane. These data permit the conclusion that strain minimization accompanies the introduction of an ether oxygen atom into a medium-sized ring.

For some years there has been keen interest in the conformational analysis of medium-sized rings.[3] Recently, attempts to analyze by means of temperature-dependent nmr spectroscopy the conformations and conformational processes occurring in cyclooctane and certain of its derivatives have been reported.[4] The conclusion has been reached[4b] that the evidence to date can best be interpreted in terms of the preferred existence of a boat–chair (**1**) and/or a twist boat–chair (**2**) conformation(s) for cyclooctane.



1 **2**

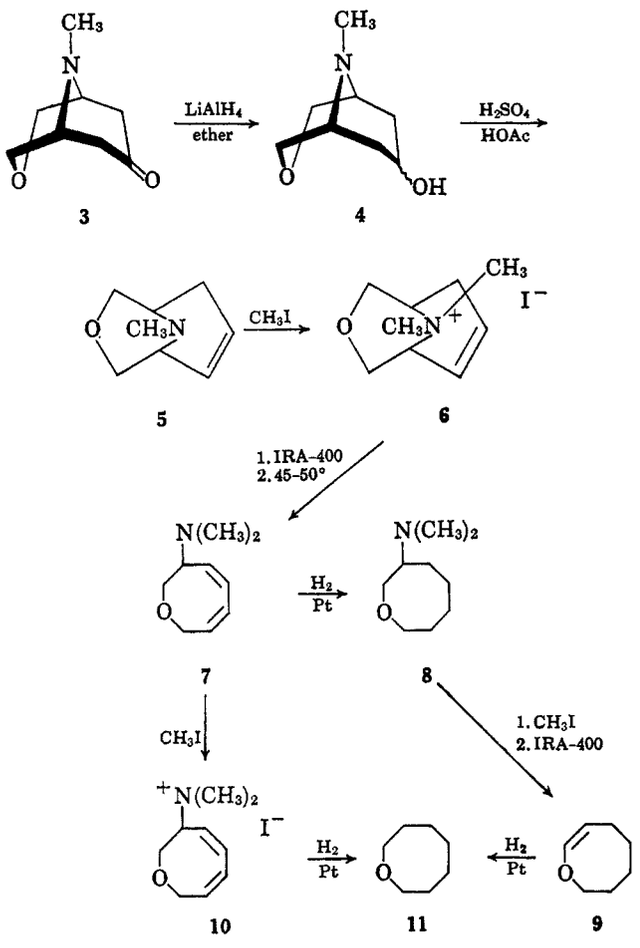
At the same time, the interesting proposal has been advanced that the conformation of eight-membered rings can be expected to remain essentially unchanged when a methylene group is replaced by a heteroatom such as oxygen.[5,6] However, recent studies in this laboratory[7] have indicated that strain minimization accompanies the replacement of a CH_2 group by O in medium-sized rings. Further demonstration of the smaller steric requirements of ether oxygen relative to a methylene group has been found in the preferred axial orientation of the *t*-butyl group in *cis*-2-alkyl-5-*t*-butyl-1,3-dioxanes.[8] In view of these divergent considerations, we have deemed it of interest to prepare oxocane, the oxygen heterocycle related to cyclooctane, and to examine its temperature-dependent nmr behavior. The present paper presents the results of this investigation.

Synthesis.—Lithium aluminum hydride reduction of the known 9-methyl-3-oxagranatanin-7-one (**3**) gave a mixture of epimeric 9-methyl-3-oxagranatanin-7-ols (**4**) in quantitative yield. Dehydration of **4** with sulfuric acid in acetic acid[9] afforded 9-methyl-3-oxagranatoline (**5**) in 88% yield. The highly crystalline methiodide **6** formed rapidly upon addition of methyl iodide to **5** in ethanol solution (99% yield). Elution of **6** through Amberlite IRA-400 ion-exchange resin (basic form) served to generate the related methohydroxide. Controlled Hofmann elimination resulted in the liberation of water and the formation of 5-dimethylamino-7-oxa-

(1) Unsaturated Heterocyclic Systems. XXVII. For XXVI, see L. A. Paquette and W. C. Farley, *J. Am. Chem. Soc.*, **89**, 3595 (1967). This work was supported in part by the Petroleum Research Fund, administered by the American Chemical Society. We express our appreciation to the donors of said fund.
(2) Alfred P. Sloan Foundation Research Fellow.
(3) For summaries of past work on this subject, see (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, Chapter 4; (b) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965.
(4) (a) J. D. Roberts, Abstracts of the 19th National Organic Symposium, Tempe, Ariz., June 1965; (b) F. A. L. Anet and M. St. Jacques, *J. Am. Chem. Soc.*, **88**, 2585 (1966); (c) F. A. L. Anet and M. St. Jacques, *ibid.*, **88**, 2586 (1966); (d) M. St. Jacques, M. A. Brown, and F. A. L. Anet, *Tetrahedron Letters*, 5947 (1966).
(5) See ref 3a, p 210.
(6) J. Dale, *J. Chem. Soc.*, 93 (1963); J. Dale, *Angew. Chem. Intern. Ed. Engl.*, **5**, 1000 (1966).
(7) L. A. Paquette and R. W. Begland, *J. Am. Chem. Soc.*, **88**, 4685 (1966).
(8) E. L. Eliel and M. C. Knoeber, *ibid.*, **88**, 5347 (1966).
(9) A. C. Cope and C. G. Overberger, *ibid.*, **70**, 1433 (1948).

1,3-cyclooctadiene (7). The ultraviolet absorption of 7, λ_{max}^{EtOH} 227 mμ (ε 5330), was in excellent agreement with the value reported for *cis,cis*-1,3-cyclooctadiene.[10] (See Scheme I.)

SCHEME I



The route to oxocane was continued from two directions. In the first and most feasible approach, diene 7 was hydrogenated catalytically to 3-dimethylaminooxocane (8), which was in turn subjected to Hofmann elimination. The exclusive product of this reaction was the enol ether 9, thus indicating that the β hydrogens α to the ether oxygen atom were preferentially removed in the transition state for elimination.[11] Hydrogenation of 9 over Adams catalyst gave oxocane (11) in good yield. Alternatively, aminodiene 7 was converted to its methiodide 10; when this substance was exposed to hydrogen over Adams catalyst, hydrogenolysis accompanied the expected hydrogenation and 11 was isolated in fair yield.

Temperature Dependent Nmr Analysis.—In general, cyclooctane and its derivatives undergo at least two changes which are visible on the nmr time scale, one near −80 to −90°, the other at about −150°.[4] Above these temperatures, spectral variations are not observed. Therefore, low-temperature nmr spectra of oxocane have been recorded.[12] At −100°, there was no apparent alteration in the absorption peaks when compared to the spectrum recorded at room temperature,[13] nor were there any changes encountered at −128 and −146°. At −160°, some slight broadening of the two peaks was encountered, but no splitting of signals was obvious. Such minimal results are most consistent with a highly flexible conformational model for oxocane (11), one in which methylene wagging, pseudo-rotation, and other ring-inversion processes have been facilitated by the introduction of the oxygen atom. We therefore conclude that, at least for the eight-membered ring case, the space requirements of an oxygen atom are, in fact, significantly less than the steric demands of a methylene group with the result that one or more very rapid averaging processes are available to 11 even at −160°.

These results are interesting in view of the quite exact parallelism which exists between tetrahydropyran and cyclohexane in their nmr properties[14] and in light of the examples which suggest that the introduction of multiple hetero atoms into a ring system generally effects an increase in the barrier to ring inversion.[15]

Experimental Section[16]

9-Methyl-3-oxagranatanin-7-ol (4).—To a flask fitted with a stirrer and condenser was added 21.3 g (0.56 mole) of lithium aluminum hydride, 1500 ml of dry ether, and 53.0 g (0.34 mole) of 3.[17] The mixture was refluxed for 14 hr and cooled. Hydrolysis was achieved by slowly adding 21.3 g of water, 21.3 g of 30% sodium hydroxide solution, and 64 g of water in that order. The slurry was filtered and the residual solid was washed thoroughly with ether. The combined filtrates were evaporated to yield 53.6 g (99.8%) of 4 as a mixture of epimers, mp 130–132° (lit.[17] mp (α isomer) 144–146°; mp (β isomer) 112–113°). The amino alcohol was not purified further at this step.

9-Methyl-3-oxagranatoline (5).—Glacial acetic acid (11.0 g) was added with cooling to 20.0 g (0.127 mole) of 4. Concentrated sulfuric acid (37 g) was added slowly with good cooling to the resulting syrup. The solution was heated at 160° for 4 hr. The reaction mixture was cooled, 120 ml of water was added, and the solution was rendered alkaline with 20% aqueous sodium hydroxide (efficient cooling). A small amount of black tar was removed by filtration and the filtrate was extracted with five 100-ml portions of chloroform. The combined organic layers were dried over magnesium sulfate and the product was distilled to give 15.5 g (88%) of clear liquid, bp 85–87° (16 mm), $n^{24}D$ 1.4960. The hydrochloride salt of 5 was prepared with ethereal hydrogen chloride and was recrystallized from ethanol–ether to provide pure white crystals, mp 234–236°.

Anal. Calcd for $C_8H_{14}ClNO$: C, 54.70; H, 8.03; N, 7.98. Found: C, 55.07; H, 8.14; N, 7.92.

9,9-Dimethyl-3-oxa-9-azoniabicyclo[3.3.1]non-6-ene Iodide (6).—A mixture of 400 ml of ethanol, 40.5 g (0.29 mole) of 5, and 142 g (1.0 mole) of methyl iodide was refluxed for 2 hr. The

(10) $\lambda_{max}^{cyclohexane}$ 228 mμ (ε 5600): A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.*, **78**, 2812 (1956). For a summary of such data, see ref 7.

(11) After completion of this work, the synthesis of 3,4,5,6-tetrahydro-2H-oxocin (9) by a totally different route appeared: F. Nerdel, J. Buddrus, W. Brodowski, and P. Weyerstahl, *Tetrahedron Letters*, 5385 (1966). The reported properties of their sample are in complete agreement with our observations.

(12) The authors wish to express their heartfelt appreciation to Professor Joseph B. Lambert of Northwestern University for his invaluable assistance in obtaining these spectra.

(13) In actuality, temperature increments of 30° were recorded between 30 and −100°. No indication of spectral modification was noted in any of the scans.

(14) J. B. Lambert, private communication.

(15) J. M. Lehn and F. G. Riddell, *Chem. Commun.*, 803 (1966); J. E. Anderson, *Quart. Rev.* (London), **19**, 426 (1965).

(16) Boiling points and melting points are uncorrected. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer fitted with sodium chloride prisms. The ultraviolet spectra were recorded on a Cary Model 14 instrument. The nmr spectra (except those at low temperature) were taken on a Varian A-60 spectrometer purchased with funds made available through the National Science Foundation.

(17) C. Zirkle, F. R. Gerus, A. M. Pavloff, and A. Burger, *J. Org. Chem.*, **26**, 395 (1961).

solution was cooled and the precipitated solid was collected by filtration. The methiodide (81.3 g, 99%) was recrystallized from aqueous ethanol to give pure white crystals, mp 305–307°.

Anal. Calcd for $C_9H_{16}INO$: C, 38.45; H, 5.74; N, 4.98. Found: C, 38.64; H, 5.83; N, 5.16.

5-Dimethylamino-7-oxa-1,3-cyclooctadiene (7).—A solution of 18.0 g (0.064 mole) of **6** in water was eluted through a column of Amberlite IRA-400 in its basic form. The alkaline eluate was evaporated *in vacuo* below 45°. The residual quaternary methohydroxide was decomposed by heating at 45–50° under a nitrogen atmosphere at 6 mm for 2 hr. The liquid which formed was taken up in ether, dried over anhydrous magnesium sulfate, and evaporated to give 7.2 g (73.2%) of yellow liquid, λ_{max}^{EtOH} 227 mμ (ε 5330). Because this material could not be distilled without rearrangement,[18] it was hydrogenated without further purification.

3-Dimethylaminooxocane (8).—A solution of 400 mg (2.6 mmoles) of **7** in 40 ml of ethyl acetate was hydrogenated at atmospheric pressure in ethyl acetate solution over Adams catalyst. Hydrogen uptake ceased after the uptake of 2 moles. The solution was filtered and evaporated and the residual liquid was distilled to give **8** as a colorless liquid, bp 97–98° (16 mm), $n^{25}D$ 1.4653. The corresponding methiodide was prepared in the usual manner and was obtained as white crystals from ethanol–ether: mp 147–148°.

Anal. Calcd for $C_{10}H_{22}INO$: C, 40.14; H, 7.41; N, 4.68. Found: C, 40.19; H, 7.18; N, 4.55.

3,4,5,6-Tetrahydro-2H-oxocin (9).—An aqueous solution of 15.0 g (0.050 mole) of the above methiodide was eluted through a column of Amberlite IRA-400 in its basic form. The alkaline eluate was concentrated under reduced pressure and the residue was distilled (with elimination beginning at *ca.* 150°) to give 1.87 g (33.4%) of **9** as a colorless liquid: bp 75–80° (15 mm); $n^{25}D$ 1.4612; $\nu_{max}^{CCl_4}$ 1650 cm^{-1} (vinyl ether); λ_{max}^{EtOH} end absorption; $\delta_{TMS}^{CCl_4}$ 1.70 (broad absorption, 6 H, H-3,4,5), *ca.* 2.16 (multiplet, 2 H, H-6), *ca.* 3.80 (multiplet, 2 H, H-2), *ca.* 4.88 (multiplet, 1 H, H-7), and 6.00 (doublet of doublets, J = 6 and 1 cps, 1 H, H-8). A sample purified by preparative gas chromatography (10 ft × 0.25 in. stainless steel column packed with 15% Carbowax 20 M on Chromosorb W, 60–80 mesh) at 118° and microredistillation was submitted for analysis.

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.03; H, 10.76.

Oxocane (11). A. Catalytic Hydrogenation of 9.—A solution of 850 mg (7.6 mmoles) of **9** in 100 ml of anhydrous ether was hydrogenated at atmospheric pressure over Adams catalyst. Hydrogen (1 mole equiv) was absorbed. The solution was filtered and the ether was carefully removed. The remaining liquid was purified by preparative gas chromatography (same column as used for **9**) and microredistillation to give 380 mg (44%) of oxocane: $n^{25}D$ 1.4486; $\delta_{TMS}^{CCl_4}$ 1.62 (broad absorption, 10 H, methylene protons) and 3.56 (broad absorption, 4 H, $-CH_2OCH_2-$).

Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.43; H, 12.29.

B. Catalytic Hydrogenation of 10.—The methiodide **10** was prepared in the usual manner. From 6.0 g (0.039 mole) of **7**, there was obtained 9.8 g (90.5%) of **10**, mp 170–171°, λ_{max}^{EtOH} 220 mμ (ε 17,100).

Anal. Calcd for $C_{10}H_{18}INO$: C, 40.69; H, 6.15. Found: C, 40.38; H, 6.45.

A solution of 885 mg (3.0 mmoles) of **10** in 30 ml of methanol was hydrogenated at atmospheric pressure over Adams catalyst. Hydrogen (~3 mole equiv) was absorbed. The solution was filtered and the methanol was carefully evaporated under reduced pressure. Ether was added to the residual oil and 330 mg of trimethylammonium iodide, mp 262–263°, was precipitated. The filtrate was evaporated to give 150 mg of oxocane (**11**) which proved to display an infrared spectrum and vpc retention times identical with those derived from the sample of part A.

Low-Temperature Nmr Spectra.—These spectra were recorded at Northwestern University with a Varian HR-60 instrument equipped with a low-temperature probe. The oxocane spectra were obtained on approximately 10% solutions of **11** in vinyl chloride with TMS as the internal standard.

Registry No.—**4**, 13145-99-8; **5**, 13146-00-4; hydrochloride salt of **5**, 13146-01-5; **6**, 13146-02-6; **7**, 13146-03-7; **8**, 13146-04-8; **9**, 13146-05-9; **11**, 6572-98-1; methiodide of **8**, 13146-17-1.

(18) This rearrangement will be described in full in a subsequent paper.

The Chlorination of Conjugated Dienamides. A New Application of the Principle of Least Motion[1,2]

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The monochlorination of some 1,3-dihydro-2H-azepin-2-ones with several reagents, *e.g.*, N-chlorosuccinimide, *t*-butyl hypochlorite, chloramine, and chlorine, is described. Chemical and spectroscopic methods reveal the site of chlorination in these cyclic dienamides to be C_4 or C_6 depending upon the substitution at N, C_3, or C_7. For example, whereas 1,3-dihydro-3,7-dimethyl-2H-azepin-2-one, 1,3-dihydro-3-*t*-butyl-7-methyl-2H-azepin-2-one, and 1,3-dihydro-1,3,7-trimethyl-2H-azepin-2-one afford exclusively the corresponding 6-chloro derivatives, 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one leads, upon chlorination, to the 4-chloro derivative as the major product (58% yield) in combination with a lesser quantity (6%) of the 6-chloro isomer. Two related dienamides, 2-pyridone and N-methyl-2-pyridone, yield the 5-chloro pyridones in good yield. A theoretical interpretation of the observed results on the basis of the principle of least motion is advanced.

In previous publications,[5] we have described the remarkable ring enlargement which is obtained upon the addition of cold ethereal chloramine to solutions of sodio 2,6-dialkylphenoxides in molten 2,6-dialkylphenols at 125–150°. Apart from the unusual nature of the ring expansion, the 1,3-dihydro-2H-azepin-2-ones which result are interesting in their own right because they embody the conjugated dienamide chromophore, >C=CC=CNC=O, an infrequently encountered and little-studied functionality. In this paper we describe the results of studies performed with the intent of investigating the mode of reaction of the conjugated dienamide unit toward chlorinating agents.

Results

To this end, treatment of 1,3-dihydro-3,7-dimethyl-2H-azepin-2-one (**1**) with a dilute solution of chlorine in carbon tetrachloride for 16 hr at 25° resulted in tar

(1) Unsaturated Heterocyclic Systems. XXIX. For XXVIII of this series, refer to L. A. Paquette and M. Rosen, *J. Am. Chem. Soc.*, **89**, 4102 (1967).

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(3) Alfred P. Sloan Foundation Research Fellow.

(4) Sinclair Oil Fellow, 1965–1966; Esso Summer Fellow, 1964.

(5) (a) L. A. Paquette, *J. Am. Chem. Soc.*, **85**, 3288 (1963); (b) *ibid.*, **84**, 4987 (1962); (c) L. A. Paquette and W. C. Farley, *ibid.*, **89**, 3595 (1967).