[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Oxepines. I. Preparation of 2,3-Dihydroöxepine and 2,3-Dihydro-6-chloroöxepine[1]

BY EDWARD E. SCHWEIZER AND WILLIAM E. PARHAM

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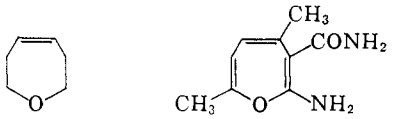
A convenient two-step synthesis of 2,3-dihydro-6-chloroöxepine (III) and 2,3-dihydroöxepine (XIV) is reported, which involves the reaction of chlorocarbenes with dihydropyran followed by subsequent pyrolysis of the cyclopropane intermediates.

In recent years there has been considerable interest in seven-membered heterocyclic systems, not only because of their relationship to certain natural products[2] but also because of the possible planarity[3] which the unsaturated derivatives may attain. Meinwald and Nozaki[3] have recently discussed this problem in their paper reporting the synthesis of 2,3,6,7-tetrahydroöxepine (I). Attempts to prepare the simple unsaturated derivatives generally have not been successful, although Westoo[4] has reported a one-step synthesis of 2-amino-3-carboxyamide-4,7-dimethyloxepine (II).

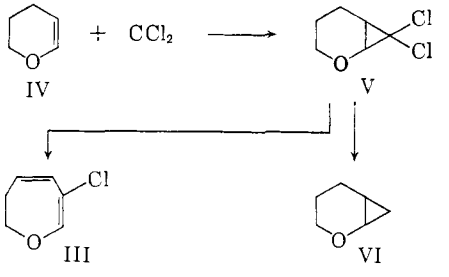


I II

We now wish to report a convenient two-step synthesis of 2,3-dihydro-6-chloroöxepine (III) and 2,3-dihydroöxepine (XIV) which involves the reaction of carbenes with cyclic vinyl ethers followed by pyrolysis of the cyclopropane adducts.

Dihydropyran (IV) was allowed to react with dichlorocarbene, produced[5] from ethyl trichloroacetate and sodium methoxide, which afforded 2-oxa-7,7-dichloronorcarane (V) in 75% yield.

2-Oxa-7,7-dichloronorcarane (V) was further characterized by its conversion (33% yield) into the known[6] 2-oxanorcarane (VI) by reduction with sodium in liquid ammonia. 2,3-Dihydro-6-chloroöxepine (III) was produced in 83% yield by heating (140–150°) a mixture of V and quinoline



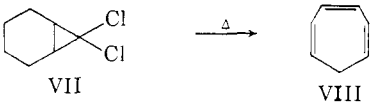
IV V III VI

under reduced pressure; the oxepine III distilled as it was formed.

2,3-Dihydro-6-chloroöxepine (III) was also prepared, in 18% yield, by the thermal degradation of 2-oxa-7,7-dichloronorcarane (V); however, at temperature above 150°, and in the presence of the hydrogen chloride produced, rapid polymerization of the oxepine III was observed which accounted for the low yield observed using this technique.[7]

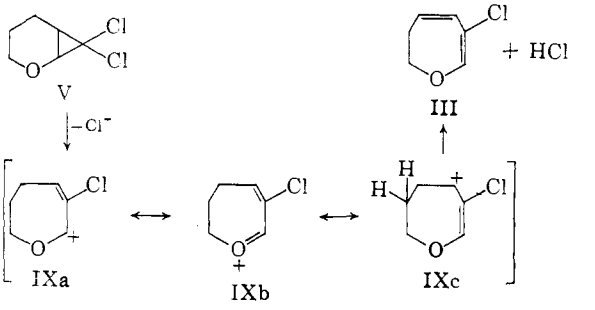
The infrared and nuclear magnetic resonance spectra of III are consistent with the structure assigned and are listed in the Experimental section. Hydrogenation of 2,3-dihydro-6-chloroöxepine (III) over platinum resulted in the uptake of four moles of hydrogen and gave 1-hexanol and hydrogen chloride.

The conversion of V to III is similar to the formation of cycloheptatriene (VIII) by thermal degradation (at 500°) of 7,7-dichloronorcarane



VII VIII

(VII).[8] The decomposition of V to III probably occurs as indicated



The initial step is assumed to involve the formation of the allylic carbonium ion IX. This intermediate (IX) is analogous to the allylic carbonium ion (XI) proposed by McElvain and Weyna[9] as an intermediate in the thermal decomposition of 2,2-dichlorocyclopropane acetals (X) to chloroacrylic esters XII and alkyl halides. Stabilization of the carbonium ion IX by resonance, as shown in IXa–c, may account for the low temperature required for this decomposition compared to that required for the conversion of VII to VIII.

The reaction of dihydropyran (IV) with chlorocarbene, produced by the method of Closs and

(1) This work was supported by a Grant (G-7382) from the National Science Foundation.

(2) R. H. F. Manske, THIS JOURNAL, **72**, 55 (1950).

(3) J. Meinwald and H. Nozaki, *ibid.*, **80**, 3132 (1958).

(4) G. Westoo, *Acta Chem. Scand.*, **13**, 604 (1959).

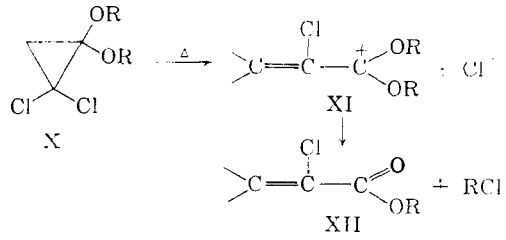
(5) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959).

(6) (a) H. E. Simmons and R. D. Smith, THIS JOURNAL, **81**, 4256 (1959). (b) The authors wish to thank H. E. Simmons for providing a spectrum of authentic 2-oxanorcarane (VI).

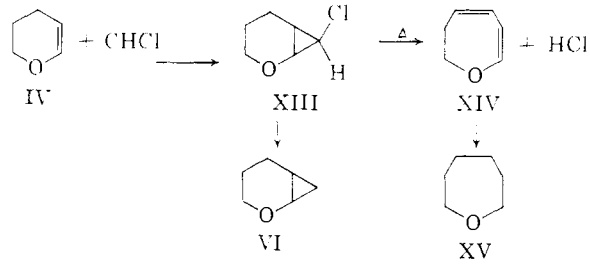
(7) The authors wish to thank H. E. Wynberg of the Central Research Department of E. I. du Pont de Nemours and Company for suggesting the use of quinoline for the conversion of V to III.

(8) H. E. Wynberg, *J. Org. Chem.*, **24**, 264 (1959).

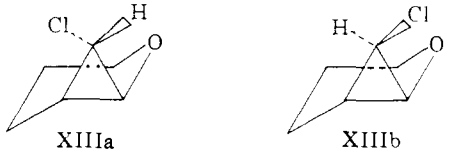
(9) S. M. McElvain and P. L. Weyna, THIS JOURNAL, **81**, 2579 (1959).



Closs,[10] gave a 28% yield of the *endo* and *exo* racemic mixtures of 2-oxa-7-chloronorcarane (X-III). Fractional distillation of the mixture gave pure samples of both racemates designated as



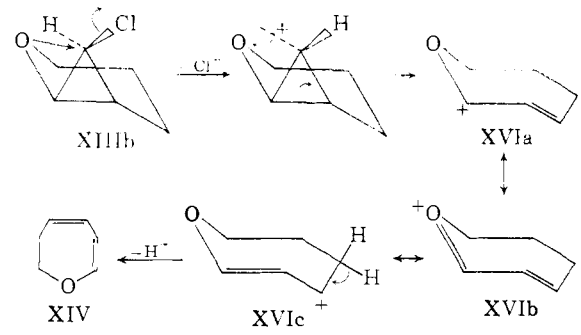
endo-2-oxa-7-chloronorcarane (XIIIa) and *exo*-2-oxa - 7 - chloronorcarane (XIIIb). These isomers were obtained in a ratio of 40/60 as calculated from refractive index data. The lower boiling isomer, which comprised approximately 40% of the reaction mixture, has been tentatively assigned structure XIIIa on the basis of the following factors.



A higher degree of steric hindrance may be expected in the transition state during the formation of the endocyclic isomer XIIIa due to the eclipsing of the ring by the large chlorine atom in chlorocarbene, than during the formation of the exocyclic isomer XIIIb due to the eclipsing of the ring by the relatively small hydrogen atom. The racemate found in greater predominance may thus be expected to be the *exo*-2-oxa-7-chloronorcarane (XIIIb).

The lower boiling isomer XIIIa could be distilled unchanged at atmospheric pressure [b.p. 176.5° (739 mm.)] either in the presence or absence of quinoline. The higher boiling isomer XIIIb decomposed at 120° at atmospheric pressure, and gave 2,3-dihydroöxepine (XIV) in 72–74% yield when distilled from quinoline at reduced pressure.

The facile conversion of the higher boiling isomer into 2,3-dihydroöxepine (XIV) is consistent with the assigned structure *exo*-2-oxa-7-chloronorcarane (XIIIb), for it is reasonable to expect anchimeric[11] (neighboring group) assistance by the *trans*-oxygen atom during the loss of the chlorine anion as shown in the equations



Subsequent loss of a proton from the intermediate XVI would yield 2,3-dihydroöxepine (XIV). Both isomers XIIIa and XIIIb were reduced with sodium in liquid ammonia and gave 60 and 70% yields, respectively, of the known[5] 2-oxanorcarane (VI).

2,3-Dihydroöxepine (XIV) was further characterized by its conversion into the known[3,12] oxepane (XV) (89% yield) by reduction with hydrogen over platinum.

Extension of this synthetic method to the preparation of dihydrothiapene, dihydroazepine, and to the corresponding benzoxepine, benthiapene and benzazepine is in progress.

Experimental

2-Oxa-7,7-dichloronorcarane (V).—Once-distilled commercial ethyl trichloroacetate (164.8 g., 0.86 mole) was added all at once to a cold (0–5°) mixture of dry dihydropyran (IV) (67.4 g., 0.8 mole), dry olefin-free pentane (600 ml.) and commercial sodium methoxide (50 g., 0.92 mole). The cold mixture was allowed to stir under an atmosphere of dry nitrogen for a period of 24 hours. Water (200 ml.) was added, the organic layer was separated and the aqueous layer was extracted twice with petroleum ether (60–68°). The organic layers were combined and dried ($MgSO_4$). The dried solution was filtered and the filtrate was concentrated on a rotary evaporator to 60° (30 mm.) The residue was distilled through a semi-micro column and 100.1 g. (75%) of compound V was obtained, b.p. 76–74° (9–8 mm.), $n^{25}D$ 1.4974. A sample, b.p. 50° (1 mm.), $n^{25}D$ 1.4975, was redistilled for analysis.

Anal. Calcd. for $C_6H_8Cl_2O$: C, 43.14; H, 4.83; Cl, 42.45; mol wt. (cryoscopic), 167. Found: C, 43.41; H, 4.85; Cl, 42.20; mol wt. (cryoscopic), 165.

2-Oxanorcarane (VI) from 2-Oxa-7,7-dichloronorcarane (V).—Compound V (6.5 g., 0.039 mole) in dry ether (20 ml.) was added dropwise, over a period of 2 hours, to a solution of sodium (5.9 g., 0.25 mole) in anhydrous liquid ammonia (approximately 45 ml.). When all of compound V had been added the liquid ammonia was allowed to evaporate while an additional 50 ml. of ether was introduced. Methanol (1 ml.) was carefully added to the mixture followed by 50 ml. of water. The solution was filtered and the layers were separated. The organic layer was washed with 50 ml. of water, dried ($MgSO_4$) and concentrated. The fraction boiling between 120–122°, $n^{25}D$ 1.4446, was collected (1.38 g.) and was shown by vapor phase chromatography to be 92% 2-oxanorcarane (VI); thus 1.27 g. (33%) of compound VI was recovered. This product was redistilled and a pure sample of 2-oxanorcarane (VI) was obtained, b.p. 122°, $n^{25}D$ 1.4488 (lit.[6] b.p. 121°, $n^{25}D$ 1.4488). The infrared spectrum of this product was identical with that of an authentic sample of 2-oxanorcarane.[6]

2,3-Dihydro-6-chloroöxepine (III).—To 18 g. of distilled quinoline was added 10 g. (0.06 mole) of 2-oxa-7,7-dichloronorcarane (V). The flask was attached to a semi-micro spiral wire column and the system was evacuated to a pressure of 78 mm. The flask was immersed in an oil-bath adjusted to 145°. Five minutes after immersion refluxing was observed; the oxepine III started to distil 12 minutes after immersion, and after 45 minutes all the oxepine III reported

(10) G. L. Closs and L. E. Closs, THIS JOURNAL, **81**, 4996 (1959).

(11) S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, *ibid.*, **75**, 147 (1953).

(12) A. Muller and W. Vanc, *Ber.*, **77B**, 669 (1944).

was recovered. The yield of 2,3-dihydro-6-chloroöxepine (III) obtained was 6.49 g. (83%), b.p. 103–107° (78 mm.), $n^{25}D$ 1.5167–1.5178.

A redistilled sample had b.p. 75° (25 mm.), $n^{25}D$ 1.5166; infrared spectrum (neat): 3019w, 2980m, 2940m, 2895m, 2820w, 1687w, 1633m, 1605s, 1465m, 1425m. 1357m, 1342m, 1292s, 1238s, 1187s, 1067m, 1040m, 973s, 923s, 885m, 851m, 802m, 734m, 642w.

The nuclear magnetic resonance spectrum, run as 10% in carbon tetrachloride with 1% tetramethylsilane as reference, gave the following: 3.36 τ, a singlet, weight 1, designated as the C-7 hydrogen; 4.23 τ, multiple, weight 1.9, C-4 and 5 hydrogens; 5.89 τ, triplet, weight 2.1, C-2 hydrogens; 7.44 τ, pseudoquad, weight 1.8, C-3 hydrogens.

Anal. Calcd. for C_6H_7ClO: C, 55.19; H, 5.40. Found: C, 54.90; H, 5.53.

Hydrogenation of 2,3-dihydro-6-chloroöxepine (III), with platinum oxide catalyst in anhydrous ether resulted in the uptake of 102% of four moles of hydrogen, and afforded a 63% yield of 1-hexanol, b.p. 80–82° (36 mm.), $n^{25}D$ 1.4163. The ethereal solution gave a chlorine test with silver nitrate and was acid to wet litmus. The infrared spectrum of the alcohol and that of an authentic sample were identical. The 3,5-dinitrobenzoates were prepared and their melting points and mixed melting points were the same.

2-Oxa-7-chloronorcarane (XIII).—Commercial butyllithium (3.54 moles) in heptane was added dropwise over a period of 4 hr. to a cold (−10 to −20°) mixture of dry dihydropyran (IV) (378 g., 4.5 moles) and dry methylene chloride (382 g., 4.5 moles). The mixture was allowed to warm to room temperature overnight. Water (600 ml.) was added, the mixture was filtered, and the organic layer was separated; the aqueous layer was extracted three times with 400-ml. portions of petroleum ether (30–60°). The organic layers were combined, dried ($MgSO_4$), and distilled. There was obtained 134 g. (28% yield) of a mixture of the racemic isomers XIIIa and XIIIb, b.p. 45° (3 mm.) to 48° (1.5 mm.), $n^{25}D$ 1.4798–1.4879. This mixture was separated by fractional distillation into the two racemates.

endo-**2-Oxa-7-chloronorcarane (XIIIa)** had b.p. 34.0° (1.1 mm.), $n^{25}D$ 1.4765; infrared spectrum (neat): shoulder 3050m, shoulder 3010m, 2950vs, 2875s, 2735vw, 1472m, 1460m, 1450m, 1404m, 1380w, 1350m, 1317w, 1285m, 1238vs, 1215vs, shoulder 1200m, 1137vs, 1115vs, 1072s, 1036s, 1015s, 990s, 955m, 938m, 883s, 848s, shoulder 827w, 812vw, shoulder 782m, 773s, 642m.

Anal. Calcd. for C_6H_9ClO: C, 54.35; H, 6.84. Found: C, 54.60; H, 7.04.

This lower boiling isomer XIIIa was distilled unchanged at atmospheric pressure (b.p. 175.5–176.5° (739 mm.), $n^{25}D$ 1.4765) in the presence and absence of quinoline.

exo-**2-Oxa-7-chloronorcarane (XIIIb)** had b.p. 48° (1.5 mm.), $n^{25}D$ 1.4873; infrared spectrum (neat): 2935–45vs, 2875vs, 2740w, shoulder 1465–1470m, 1457s, 1444s, 1394s, shoulder 1378–1382m, 1357s, 1338m, 1321m, 1287vs, 1243vs, 1220vs, 1145vs, 1110vs, 1075vs, 1047vs, 990m, 973vs, 915s, 878s, 847m, 792s, 756m, 733vs, 701vs, 672s.

Anal. Calcd. for C_6H_9ClO: C, 54.35; H, 6.84. Found: C, 54.45; H, 6.84.

This isomer XIIIb decomposed upon attempted distillation at atmospheric pressure, and afforded a high yield of 2,3-dihydroöxepine (XIV) when distilled from quinoline.

The composition of the original mixture XIII was calculated to be composed of approximately 40% *endo*-2-oxa-7-chloronorcarane (XIIIa) and 60% *exo*-2-oxa-7-chloronorcarane (XIIIb) by use of refractive index data.

2-Oxanorcarane (VI) from *endo*-2-oxa-7-chloronorcarane (XIIIa) was obtained from a sample (4 g.) of the *endo*-racemic mixture XIIIa, b.p. 34.0° (1.1 mm.), $n^{25}D$ 1.4768. The procedure was essentially the same as that described for the conversion of V to VI except that 1.2 g. of sodium was employed in approximately 25 ml. of anhydrous liquid ammonia. The crude product weighed 2.15 g. (b.p. 121–122°, $n^{25}D$ 1.4200–1.4450) and was shown to be 82% 2-oxanorcarane (VI) by vapor phase chromatographic analyses. Thus 1.76 g. (60%) of 2-oxanorcarane (VI) was present. A redistilled sample of this product had b.p. 122°, $n^{25}D$ 1.4486 (lit.[6] b.p. 121°, $n^{25}D$ 1.4488), and its infrared spectrum was identical with that of an authentic sample of 2-oxanorcarane (VI).[6]

2-Oxanorcarane (VI) from *exo*-2-oxa-7-chloronorcarane (XIIIb) was obtained from a sample (4.2 g.) of the *exo*-racemic mixture XIIIb, b.p. 47–48° (1.6–1.7 mm.), $n^{25}D$ 1.4861. The procedure was essentially the same as that described above (1.8 g. of sodium was employed). The crude product weighed 2.40 g. (b.p. 120–122°, $n^{25}D$ 1.4457–1.4487) and was shown to be 91% 2-oxanorcarane (VI) by vapor phase chromatographic analyses. Thus 2.18 g. (70%) of 2-oxanorcarane (VI) was present. A redistilled sample of this product had b.p. 122°, $n^{25}D$ 1.4487 (lit. b.p. 121°, $n^{25}D$ 1.4488), and its infrared spectrum was identical with that of an authentic sample of 2-oxanorcarane (VI).[6]

2,3-Dihydroöxepine (XIV).—To 20 g. of distilled quinoline was added 10 g. (0.075 mole) of *exo*-2-oxa-7-chloronorcarane (XIIIb racemates). The flask was attached to a semi-micro spiral wire column and the system was evacuated to a pressure of 156 mm. The flask was immersed in an oil-bath set at 150°. Distillation of the 2,3-dihydroöxepine (XIV) as it was formed yielded 5.4 g. (74%), b.p. 94–62° (150–156 mm.), $n^{25}D$ 1.4940–1.4950. A redistilled sample had b.p. 61° (100 mm.), $n^{25}D$ 1.4965; infrared spectrum (neat): 3040m, 2985w, 2940m, 2915m, 2830ww, 1641m, 1611s, 1467w, 1433w, 1403w, 1370vw, 1341w, 1302s, 1232w, 1203w, 1120s, 1063vw, 1037vw, 979w, 920m, 882w, 773w, 718s, 635w.

The nuclear magnetic resonance spectrum, run the same as the chloroöxepine III, had: at 3.69 τ, doublet, weight 1.35, assigned to the hydrogen at the 7-position; 4.32 τ, pseudo-doublet, wt. 2.4, 4- and 5-hydrogens; 5.23 τ, triplet, wt. 1, 6-hydrogen; 5.89 τ, intense triplet, wt. 1.86, 2-hydrogen; 7.47 τ, pseudoquadruplet, 7-hydrogen.

Anal. Calcd. for C_6H_8O: C, 74.97; H, 8.39. Found: C, 74.71; H, 8.58.

Hydrogenation of 2,3-dihydroöxepine (XIV) over platinum oxide resulted in a 97% uptake of two moles of hydrogen. An 89% yield of oxepane XV was obtained: b.p. 119–120.5° (740 mm.), $n^{25}D$ 1.4351. The pure material had b.p. 121° (741 mm.), $n^{25}D$ 1.4365 (lit.[12] b.p. 119–120°, $n^{25}D$ 1.4393; lit.[3] $n^{24}D$ 1.4361).

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

Seven-Membered Heterocyclic Systems. II. The Synthesis of 2,3-Dihydroöxepine[1]

BY JERROLD MEINWALD,[2] DAVID W. DICKER AND NAFTALI DANIELI

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Two routes to a cyclic diene from 2,3,6,7-tetrahydroöxepine are described. This diene is shown to be 2,3-dihydroöxepine, rather than the expected 2,7-dihydroöxepine, on the basis of its physical properties and its acid lability.

Introduction.—The synthesis of 2,3,6,7-tetrahydroöxepine (I) has been described in a recent publication from this Laboratory.[3] Interest in this compound stemmed from its possible utilization as an intermediate in the synthesis of the as

(1) This research was supported by a Research Grant from the National Institutes of Health. This support is gratefully acknowledged.

(2) Fellow of the Alfred P. Sloan Foundation.

(3) For the previous paper in this series, see J. Meinwald and H. Nozaki, THIS JOURNAL, **80**, 3132 (1958).