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Chemistry of 1,3-Dioxepins. II[1]. Dehydrohalogenation of 5,6-Dihalogen-1,3-Dioxepanes with Strong Bases

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Dehydrohalogenation of 5,6-dihalogen-1,3-dioxepanes II with KOH/MeOH or $NaOCH_3$/MeOH under controlled reaction conditions gave mainly 5-halogen-4,7-dihydro-1,3-dioxepines III. Further substitution of vinylic-bromine in III whit KO-*t*-Bu/*tert*-BuOH or KOH/MeOH led to corresponding 5-substituted-4,7-dihydro-1,3--dioxepines some of which underwent spontaneous isomerization to 6,7-dihydro-1,3-dioxepines. Substitution of vinylic-bromine appeared to follow an elimination-addition mechanism with initial formation of an intermediate with a triple bond.

Published data on dehydrohalogenation of 5,6-dihalogen-1,3-dioxepanes II with strong bases demonstrate relatively easy dehydrohalogenation of one halogen atom giving mainly 5-halogen-4,7-dihydrodioxepines III.[2-5] Substitution of halogen from dioxepines III has not yet been described, nor the mechanism determined. On the other hand, substitution of vinylic-halogen from equally sized seven membered ring 1-halocycloheptenes with strong bases is a well studied reaction in which halogen is substituted by three elimination--addition mechanisms *i*) *via* cycloheptyne, *ii*) *via* 1,2-cycloheptadiene, and *iii*) *via* prototropic rearrangement to 3-halocycloheptene followed by dehydrohalogenation to cycloheptadiene.[6-8]

In order to obtain more information about the behaviour of 5,6-dihalogendioxepanes II and 5-halogen-4,7-dihydrodioxepines III when treated with strong bases, as well as to clarify the mechanism of vinylic-bromine substitution in the 4,7-dihydro-1,3-dioxepine series, we undertook a study of the reaction of dihalogendioxepanes II and 5-bromo-4,7-dihydrodioxepine IIIb with strong

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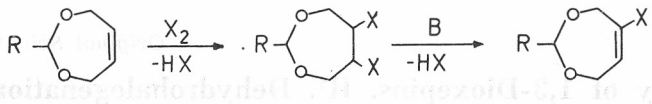
bases (sodium and potassium hydroxide, sodium methoxide, and potassium *tert*-butoxide).

Scheme 1

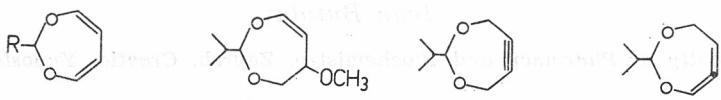


I II III

a) R=H
b) R=*iso*-Pr

a) X=Br; R=H
b) X=Br; R=*iso*-Pr
c) X=Cl; R=H
d) X=Cl; R=*iso*-Pr

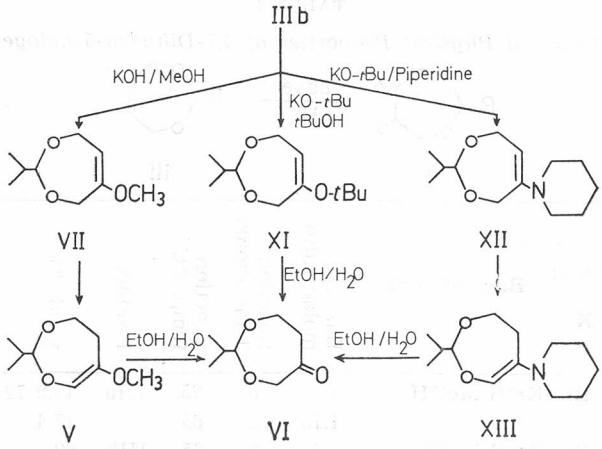
a) X=Br; R=H
b) X=Br; R=*iso*-Pr
c) X=Cl; R=H
d) X=Cl; R=*iso*-Pr



IV VIII IX X

a) R=H
b) R=*iso*-Pr

Addition of bromine to Ib in tetrachloromethane or chloroform gave dibromide IIb in 72.4% yield. Dehydrobromination of IIb was effected with potassium hydroxide in boiling methanol for 1 to 3 hours. After removal of solids and methanol the residue was fractionated *in vacuo* into two fractions. The first fraction, b. p. 40—70 °C/2.7 kPa, gave on redistillation pure diene IVb as a pale-yellow liquid with b. p. 50 °C/2.7 kPa in 7—8% yield. Gas-liquid chromatography of the reaction mixture showed 10—20% yield of diene IVb, thus a lot of IVb is lost during the isolation process. The ^{1}H NMR spectra of IVb show a well resolved AA'BB' system at 4.8 and 6.4 ppm of protons on C-4 and C-7. These are quite similar to those of 1,3-dioxepine IVa[3] and to C-4 and C-7 protons of 1,3-dithiepin anion.[9] The second fraction with b. p. 80—96 °C/2.7 kPa gave on redistillation two fractions with b. p. 90—95 °C/2.4 kPa and b. p. 95—96 °C/2.4 kPa. The latter was identified as pure 5-bromo-4,7-dihydrodioxepine IIIb (56% yield). The fraction with b. p. 90—95 °C/2.4 kPa separated by column chromatography on silica, gave two compounds identified as 6,7-dihydro-2-isopropyl-5-methoxy-1,3-dioxepine (V) and 2-isopropyl-1,3-dioxepan-5-on (VI). The structure of methoxydioxepine V and ketone VI were assigned from spectral data. Thus methoxydioxepine V exhibited one proton singlet in ^{1}H NMR at 6.27 ppm for the C-4 proton[10] and a very weak IR absorbance at 1660 cm^{-1} for the C=C double bond, characteristic for 6,7-dihydrodioxepins. The ketone VI showed strong IR absorption for carbonyl at 1720 cm^{-1} and gave a MS peak for the parent ion of m/e 158. Additional structural evidence for V, as well as an explanation for the ketone VI formation, was given by hydrolysis of V to ketone VI with aqueous ethanol (Scheme 2).



Elimination of the first bromine in dibromodioxepane IIb was found to be faster than elimination of the second one. The effect is illustrated in Figure 1.

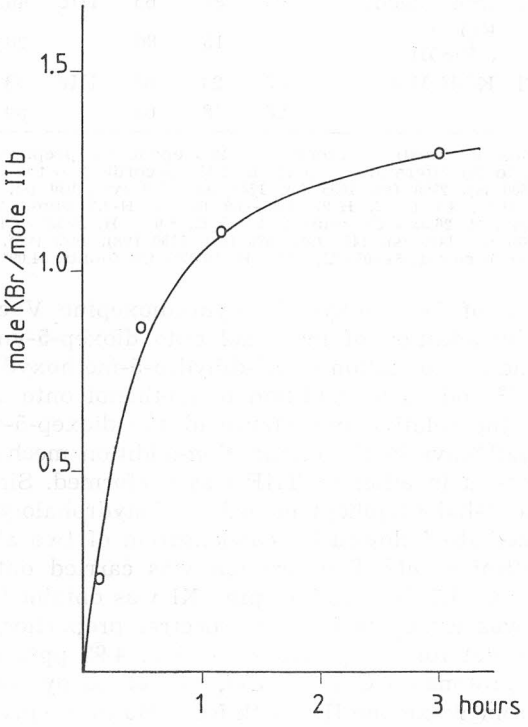
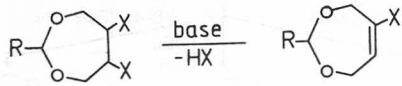


Figure 1. Formation of KBr as a function of time during dehydrobromination of IIb with KOH/MeOH at a starting molar ratio KOH/IIb of 1.5

Under controlled reaction conditions (time, molar ratio of II and base) some monohalogen dioxepines III were isolated in yields indicated in Table I.

TABLE I

Reaction Conditions and Physical Properties of 4,7-Dihydro-5-halogen-1,3-dioxepines



II III

	Dioxepane II R	X	Base/solvent	Base[a]/II molar ratio	Reaction Time (hour)	Reaction temp. (°C)	Product	yield[b] %	b. p. °C/kPa
IIa[c]	H	Br	KOH/MeOH	1	6	65	IIIa	15.9	72—76/2.3 (70/1.47[3])
				1.75	12	65		15.4	
IIb	iso-Pr	Br	KOH/MeOH	1.5	3	65	IIIb	69	94—96/2 (95/2[5])
				2.5	3	65		50.4	
			NaOH/MeOH	2.0	2	65		20.1	
			$NaOCH_3$/MeOH	2.0	1	65		29.6	
IIc[c]	H	Cl	KOH/MeOH	2.5	88	65	IIIc	46.6	57/2[d]
			KO *t*Bu/ *t*-BuOH	1.1	15	80		20.3	
IId[c]	iso-Pr	Cl	KOH/MeOH	1.5	24	65	IIId	53.0	88/2[e] (90—100/2.5[5])
				2.5	48	65		50	

[a] molar ratio; [b] yields of redistilled product; [c] Dioxepane IIa prepared according to literature,[2] IIb, according to the literature[5] and IIc and IId according to the literature.[1] [d] IR (neat): 3050 (w) 2950(m), 2880 (s), 2790 (v), 1655 (s), 1245 (s), 1130 (vs), 930 (s), 785 (s) cm^{-1}. ^1H NMR (CCl_4): 5.72 (m, 1, H-6), 4.7 (s, 2, H-2), 4.35—3.9 (m, 4, H-4,7 ppm. Anal. $C_5H_7ClO_2$ (134.562) calc'd: 44.63% C, 5.24% H, 26.35% Cl, found: 44,50% C, 5.03% H, 26.18% Cl. [e] IR (neat): 3050 (w), 2970 (s), 2880 (s), 1670 (s), 1480 (s), 1455 (s), 1320 (m), 1150 (vs), 1025 (vs), 955 (m), 800 (m) cm^{-1}. Anal. $C_8H_{13}ClO_2$ (176.639) calc'd: 54.40% C; 7.42% H; 20.07% Cl, found: 54.09% C; 7.60% H; 20.30% Cl.

The formation of 5-methoxy-6,7-dihydrodioxepine V could be explained in two ways, *i*) by addition of methanol onto dioxep-5-yne intermediate IX followed by π-bond isomerization of 4,7-dihydro-5-methoxydioxepine VII under basic conditions[11,12] and *ii*) by addition of methanol onto allene intermediate X. To determine the relative importance of the dioxep-5-yne IX and allene X intermediate pathways in the elimination-addition mechanism, the reaction of IIIb with KO-*t*-Bu in ether or THF was performed. Similar reaction conditions applied to 1-halocycloheptene led to dehydrohalogenation mainly *via* the allene intermediate followed by condensation of two allene intermediates as shown by Bottini *et al.*[7] The reaction was carried out at 70° C for two hours and 5-*t*-butoxy-4,7-dihydrodioxepine XI was obtained in 60% yield. The structure of XI was established by its spectral properties, notably ^1H NMR spectra with a triplet for the proton on C-6 at 4.92 ppm and a multiplet at 4.4—3.5 ppm for protons on C-4 and C-7, as well as hydrolysis to the ketone VI. Reaction of bromodioxepine IIIb with KO-*t*-Bu in the presence of piperidine gave 5-piperidyl-4,7-dihydrodioxepine XII in 62% yield. IR spectra taken immediately after isolation show a very strong IR absorption of C=C double bond at 1645 cm^{-1}. The ^1H NMR spectra taken one hour after isolation show to be a mixture of isomers XII and XIII (2 : 1 ratio) with a triplet at 4.7 ppm for the C-6 proton of isomer XII (5-piperidyl-4,7-dihydrodioxepine). After stan-

ding for 15 hours at room temperature, XII fully isomerized into 5-piperidyl-6,7-dihydrodioxepine XIII. The ^{1}H NMR spectra taken after 15 hours show to be pure XIII isomer with one proton singlet at 6.00 ppm for the C-4 proton.[10] The isomerization of XII to XIII was followed qualitatively by inspection of the IR spectra, particularly by the disappearance of a very strong absorbance of a C=C double bond, characteristic for 5-substituted-4,7-dihydrodioxepines, at 1645 cm^{-1} (Figure 2).

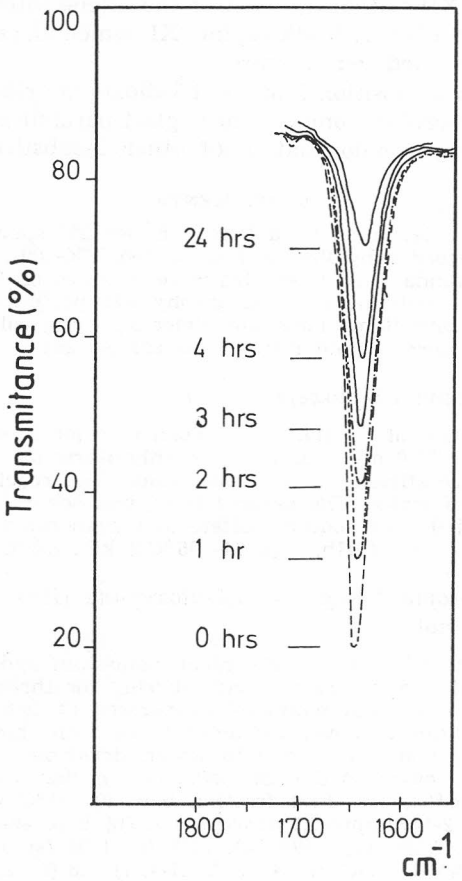


Figure 2. Changes of transmittance of C=C double bond absorbance at 1645 cm^{-1} during isomerization of 4,7-dihydro-5-(*N*-piperidyl)-1,3-dioxepine XII to 6,7-dihydro-5-(*N*-piperidyl)-1.3--dioxepine XIII

In the light of these results, the reaction of bromodioxepane IIb with sodium methoxide in methanol was examined in an attempt to obtain evidence for the formation of 5-methoxy-4,7-dihydrodioxepine VII. After refluxing the reaction mixture for 24 hours the solid material and methanol were removed and the residue fractioned in vacuo. One of the fractions gave compound without bromine, showing a strong IR absorption of a C=C double bond at 1650 cm^{-1}, characteristic for 5-substituted-4,7-dihydrodioxepins. Upon further purification by column chromatography, or bystanding, isolated product gave exclusively 5-methoxy-6,7-dihydrodioxepine V. This lead to the conclusion

that the primary isolated product was 5-methoxy-4,7-dihydrodioxepine VII which isomerized upon standing.

Briefly, the reaction of 5-bromo-1,3-dioxepine IIIb with strong bases appears to follow an elimination-addition mechanism with initial dehydrohalogenation to the corresponding dioxep-5-yne IX. No product was isolated that would indicate prototropic rearrangement. The formation of 6,7-dihydrodioxepines V and XII is the result of spontaneous isomerization of 4,7-dihydrodioxepines VII and XII without impact of the allene intermediate. The exception was 5-*t*-butoxy-4,7-dihydrodioxepine XI which does not isomerize even after 48 hours at elevated temperature.

The substitution at position 2 of the 1,3-dioxepine ring may influence chemical propertioes. Therefore, one cannot neglect paralell participation of allene intermediates in dehydrohalogenation of other 2-substituted 5-halogendioxepins.

EXPERIMENTAL

IR spectra were determined by a Perkin Elmer 257 spectrophotometer, and ^{1}H NMR spectra were recorded by Varian T-60 or Jeol FX-100 in $CDCl_3$ or CCl_4 using TMS as an internal standard. Mass spectra were recorded on Varian CH-7 or Varian Mat 112 S at 70 eV. Gas-liquid chromatography was performed on a Perkin Elmer F-30 Mod. equipped with flame ionisation detector, using column 2 × 0.003 m with 5% OV-17 on Chromosorb W and nitrogen as carrier gas.

5,6-Dibromo-2-isopropyl-1,3-dioxepane (IIb)

To a stirred solution of Ib[2] (142.2 g, 1 mole) in chloroform (180 mL), was added a solution of bromine (55.6 mL, 1.02 mole) in chloroform (60 mL) at 10 °C over two hours and the mixture stirred for one more hour. The reaction mixture was then poured into 500 mL of water. The organic layer was separated, washed twice with 150 mL of water, dried over sodium sulfate and evaporated. The residue gave on distillation 218.7 g (72.4%) of IIb, b. p. 94—96 °C/2 kPa (95 °C/2 kPa ref. 5).

Reaction of 5,6-Dibromo-2-isopropyl-1,3-dioxepane (IIb) with Potassium Hydroxide in Methanol

Dibromodioxepane IIb (148 g, 0.485 mole), potassium hydroxide (68 g, 1.2 mole) and methanol (625 mL) were refluxed with stirring for three hours. Solid material was removed by filtration and methanol evaporated at 20.0 kPa. Water (100 mL) was added to the residue and was extracted twice with chloroform (100 mL). The extracts were combined and washed with water, dried over anhydrous magnesium sulfate and the solvent evaporated at 20.0 kPa. The residue was fractionated at 2 kPa (bath temperature 100 °C). The first fraction b. p. 40—94 °C was redistilled to give 4.6 g (7.6%) of pure *2-isopropyl-1,3-dioxepine* (IVb) b. p. 49—51 °C. IR (neat): 3060 (m), 2970 (s), 2910 (s), 1620 (vs), 1595 (w), 1425 (s), 1390 (s), 1280 (vs), 1145 (vs), 895 (s), 740 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$): 6.4 (m, 2, H-4, 7), 4.8 (m, 2, H-5, 6) 4.5 (d, 1, H-2), 2.0 (m, 1, iso-PrCH), 1.0 (d, 6, iso-$PrCH_3$) ppm. MS : M$^+$ 141 e/v.

Anal. $C_8H_{12}O_2$ (140,18) calc'd: C 68.54; H 8.63%
found: C 68.56; H 8.52%

The second fraction (64.5 g) b. p. 94—115 °C gave on fractionation 5.2 g of oil product with b. p. 90—98 °C/2.4 kPa, and 56.4 g of *5-bromo-2-isopropyl-4,7-dihydro-1,3-dioxepine* (IIIb) (50.4%), b. p. 94—96 °C/2 kPa. IR (neat): 2960 (s), 2930 (s), 2910 (s), 2880 (s), 1650 (s), 1470 (s), 1450 (s), 1395 (s), 1135 (vs), 940 (s), 780 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): 5.93 (t, 1, H-6), 4.67—3.67 (m, 5, H-4, 7 and H-2), 1.87 (m, 1, iso-PrCH). 0.9 (d, 6, iso-$PrCH_3$) ppm.

Anal. $C_8H_{13}BrO_2$ (221.09) calc'd: C 43.46; H 5.93; Br 36.14%
found: C 43.45; H 6.20; Br 36.01%

The oil product with b. p. 90—98 °C was chromatographed through a silica column using benzene as eluent. The benzene eluates afforded *6,7-dihydro-2-iso-*

propyl-5-methoxy-1,3-dioxepine (V) (0.2 g), b. p. 86—88 °C/2.4 kPa, *and 2-isopropyl--1,3-dioxepan-5-on* (VI) (0.3 g), b. p. 94—96 °C/2 kPa.

V: IR (neat): 3080 (w) 2980 (s), 2960 (s), 1660 (vw), 1450 (m), 1380 (m), 1240 (s), 1210 (vs), 1150 (vs), 1090 (s), 790 (m) cm^{-1}. ^1H NMR ($CDCl_3$): 6.27 (s, 1, H-4), 4.08 (d, 1, H-2), 4.0—1.85 (m, 4, H-6, 7), 3.47 (s, 3, OCH_3), 2.2—1.4 (m, 1, iso-PrCH), 0.94 (d, 1, iso-$PrCH_3$) ppm.

Anal. $C_9H_{16}O_3$ (172.227) calc'd: C 62.77; H 9.37%
found: C 62.53; H 9.31%

VI: IR (neat): 2960 (s), 2870 (s), 1720 (s), 1470 (m), 1255 (s), 1190 (m), 1160 (s), 1120 (vs), 1060 (s) cm^{-1}. ^1H NMR (CCl_4): 4.3—2.3 (m, 7 H-2, H-4, H-6, H-7), 2.2—1.5 (m, 1, iso-PrCH), 0.95 (d, 6, iso-$PrCH_3$) ppm.

Anal. $C_8H_{14}O_3$ (158.20) calc'd: C 60.81; H 8.86%
found: C 60.76; H 8.79%

Reaction of 5-bromo-4,7-dihydro-2-isopropyl-1,3-dioxepine (IIIb) with Sodium Methoxide in Methanol

5-bromo dioxepine IIIb (11.0 g; 0.05 mole), sodium methoxide (prepared from 3.45 g; 0.15 mole sodium) and methanol (75 mL) were refluxed for 24 hours. After cooling, solid material was removed by filtration and methanol evaporated *in vacuo*. The residue was extracted twice with ether (30 mL), and extract fractionated. The fraction with b. p. 92—97 °C/24 kPa (4 g) was redistilled giving 1.9 g of *4,7-dihydro--2-isopropyl-5-methoxy-1,3-dioxepine (VII)* with b. p. 88—91 °C/2.4 kPa. IR (neat): 2960 (s), 2900 (s), 2870 (s), 1650 (s), 1470 (s), 1440 (s), 1390 (s), 1360 (s), 1130 (vs), 1005 (s), 1780 (m).

Column chromatography of VII on silica using benzene as eluent gave 6,7-dihydro-2-isopropyl-5-methoxy-1,3-dioxepine (V).

5-tert.-Butoxy-4,7-dihydro-2-isopropyl-1,3-dioxepine (XI)

To a stirred suspension of KO-*t*-Bu (4.6 g, 0.04 mole) in THF (35 mL) at 70 °C was added dropwise over 20 min a solution of IIIb (3.9 g, 0.018 mole) in THF (10 mL). After two hours the reaction mixture was cooled and quenched with 20 mL saturated potassium carbonate solution. The mixture was poured into 50 mL water and extracted with ether (2 × 30 mL). The ether extract was washed with potassium carbonate solution, dried over anhydrous potassium carbonate and distilled to give XI, 2.4 g (62.2%), b. p. 68 °C/0.13 kPa. IR (neat): 2970 (s), 2950 (s), 2870 (s), 1655 (s), 1470—1430 (broad), 1390 (s), 940 (m), 870 (s) cm^{-1}. ^1H NMR (CCl_4): 4.92 (t, 1, H-6), 4.19 (d, 1, H-2), 4.4—3.5 (m, 4, H-4, 7), 2.15—1.45 (m, 1, iso-PrCH), 1.32 (s, 9, tert.-Bu), 0.9 (d, 6, iso-$PrCH_3$) ppm.

Anal. $C_{12}H_{22}O_3$ (214.307) calc'd: C 67.25; H 10.35%
found: C 67.08; H 10.08%

Reaction of 5-bromo-4,7-dihydro-1,3-dioxepine (IIIb) with KO-t-Bu in Presence of Piperidine

To a stirred suspension of KO-*t*-Bu (2.3 g, 0.02 mole) in dry ether (15 mL) at room temperature was added at once a solution of IIIb (3.3 g, 0.0149 mole) in 10 mL of piperidine. The reaction mixture came to boiling and after 30 min the solvent was evaporated *in vacuo*. The residue was mixed with benzene (20 mL), the solid filtered off, and the solution distilled *in vacuo* to give 2.1 g (62.4%) of *4,7-dihydro--2-isopropyl-5(N-piperidyl)-1,3-dioxepine* (XII), b. p. 97—100 °C/0.11 kPa. IR (neat): 3060 (w), 2950 (vs), 2930 (vs), 2850 (s), 1645 (s), 1470 (s), 1450 (s), 1440 (s), 1390 (s), 1225 (s), 1190 (s), 1020 (m), 860 (m), 755 (w) cm^{-1}.

After standing for 24 hours XII isomerized to *6-7-dihydro-2-isopropyl-5-(N--piperidyl)-1,3-dioxepine* (XIII), b. p. 104 °C/0.13 kPa. IR (neat): 3070 (w), 2950 (vs), 2930 (vs), 2850 (s), 1640 (vw), 1380 (s), 1365 (m), 1270 (m), 1230 (s), 1190 (s), 1170 (vs), 1000 (m), 755 (w) cm^{-1}. ^1H NMR (CCl_4): 6.0 (s, 1, H-4), 4.3—1.2 (m, 6, H-2, H-6, H-7, iso-PrCH), 2.6 (s, 4, $PipCH_2$—N—CH_2), 1.55 (s, 6, $Pip(CH_2)_3$), 0.93 (d, 6, iso-$PrCH_3$) ppm.

Anal. $C_{13}H_{23}NO_2$ (225.32) calc'd: C 69.29; H 10.29; N 6.22%
found: C 69.12; H 10.22; N 6.40%

2-Isopropyl-1,3-dioxepane-5-on (VI)

A) 6,7-Dihydro-2-isopropyl-5-methoxy-1,3-dioxepine (V) (0.5 g 0.0029 mole) was boiled in 80% ethanol (5 mL) for three hours. The solvent was evaporated leaving 0.27 g (58.8%) of VI, the spectra of which were identical with those of ketone VI isolated from the reaction mixture of IIIb with KOH in methanol.

B) 5-*tert*-Butoxy-4,7-dihydro-2-isopropyl-1,3-dioxepine (XI) (1.3 g, 0.0061 mole) was boiled in 80% ethanol (10 mL) for seven hours. The solvent was evaporated *in vacuo* and 0.8 g (83.4%) of crude ketone VI was obtained. It was purified by distillation giving 0.6 g (62.5%) of pure VI, b. p. 55—58 °C/0.13 kPa.

C) 6,7-Dihydro-2-isopropyl-5-(*N*-piperidyl)-1,3-dioxepine (XIII) (1.4 g, 0.0062 mole) was boiled in 80% ethanol (25 mL) for three hours. The solvent was evaporated and the residue distilled giving 0.6 g (61%) of ketone VI, b. p. 55—58 °C/0.13 kPa.

General Procedure for Preparing 5-halogen-4,7-dihydro-1,3-dioxepines III

Dihalogen dioxepane II (0.2 mole), base (molar ratio to II indicated in Table I) and methanol (100—150 mL) were refluxed with stirring for the time indicated in the Table. The solid material was filtered off and methanol evaporated *in vacuo*. Water (100 mL) was added and extracted with chloroform (2 × 60 mL). The combined extracts were washed with water (2 × 30 mL) and dried over anhydrous magnesium sulfate. After removal of the solvent the crude mixture was fractionated *in vacuo* to give 5-halogenidoxepines III in yields indicated in the Table.

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SAŽETAK

Kemija 1,3-dioksepina. II. Dehidrohalogeniranje 5,6-dihalogen-1,3-dioksepana s jakim bazama

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Kod kontroliranih reakcijskih uvjeta dobiveni su dehidrohalogeniranjem 5,6-dihalogen-1,3-dioksepana II sa KOH/MeOH ili $NaOCH_3$/MeOH odgovarajući 5-halogen-4,7-dihidro-1,3-dioksepini III.

Daljnjom reakcijom vinilnog broma iz III s KO-*t*-Bu/BuOH ili KOH/MEOH nastaju odgovarajući 5-supstituirani-4,7-dihidro-1,3-dioksepini od kojih neki spontano izomeriziraju u 6,7-dihidro-dioksepine. Supstitucija vinilnog halogena ide putem eliminacije — adicije preko međuprodukta s trosktrukom vezom.