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Chemistry of 1,3-Dioxepins. I. Reaction of 4,7-Dihydro--1,3-dioxepins with Nitryl Chloride

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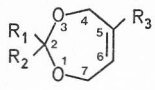
The reaction of 4,7-dihydro-1,3-dioxepins II with nitryl chloride in chloroform of light petroleum as a solvent gave a mixture of 5-chloro-6-nitro-dioxepans III and 5,6-dichloro-dioxepans IV. In alkylnitriles as solvents, the corresponding 6-acylamino-5-chloro--dioxepans VII were also formed. Hydrodechlorination of III in the presence of triethylamine afforded 5-nitro-4,7-dihydro-1,3-dioxepins I.

For use in studying substituent effects in position 5 of the 4,7-dihydro-1,3-dioxepine ring on a Diels-Alder reaction with oxazoles as diene component, we were interested in preparing the hitherto unknown 5-nitro-1,3-dioxepins I. In view of the known easy hydrodechlorination of vicinal chloro-nitro-compounds, 5-chloro-6-nitro-dioxepans III appeared to be attractive precursors of nitro-dioxepins. We paid special attenation to the possibility of one-step preparation of chloro-nitro-dioxepans III from dioxepins II and the readily available nitryl chloride[1]. This paper describes the reaction of dioxepins II with nitryl chloride and preparation of 5-nitro-dioxepins I.

It has been reported[1-6] that nitryl chloride with olefinic substrates gave chloro-nitro-derivatives in a mixture with other addition products, the ratio of which varied with reaction conditions (temperature, solvent) and with the nature of olefin.

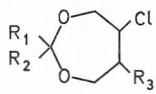
In our experiments, dioxepins II were allowed to react with nitryl chloride at — 50 to 40 °C in inert organic solvents, to give a crude product consisting mainly of two components shown by GLC (separated by fraction distillation) identified as 5-chloro-6-nitro-dioxepans III and 5,6-dichloro-dioxepans IV. In light petroleum, heptane, or tetrachloromethane at 20 °C III was obtained in 30—40% while in ether, chloroform or dichloromethane in 6—20% yield.

The structure of chloro-nitro-dioxepan IIIa was assigned from spectral data, notably by its IR absorptions for the nitro group on saturated carbon at 1550 and 1350 cm^{-1}. Chloro-nitrodioxepan IIIb contained an unidentified »nitrate« with the characteristic IR absorptions at 1645 and 1275 cm^{-1}, which could not be fully removed by repeated distillations and/or column separations. Although the analytical data obtained were not accurate, the NMR and IR spectra of IIIb were in agreement with the proposed structure. Chemical sup-



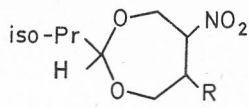
I a $R_1=R_2=H$, $R_3=NO_2$
b $R_1=H$, $R_2=$iso-Pr, $R_3=NO_2$

II a $R_1=R_2=R_3=H$
b $R_1=R_3=H$, $R_2=$iso-Pr
c $R_1-R_2=-(CH_2)_5-$, $R_3=H$



III a $R_1=R_2=H$, $R_3=NO_2$
b $R_1=H$, $R_2=$iso-Pr, $R_3=NO_2$

IV a $R_1=R_2=H$, $R_3=Cl$
b $R_1=H$, $R_2=$iso-Pr, $R_3=Cl$
c $R_1-R_2=-(CH_2)_5-$, $R_3=Cl$

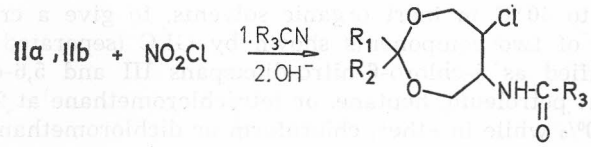


V $R=NHC_6H_5$
VI $R=NO$

port for the structure IIIb was provided by the reaction with aniline to give 5-phenylamino-6-nitro-dioxepan V. The NMR spectra of IIIa and IIIb showed two broad unresolved multiplets at 4.2 and 4.7 ppm of protons on C-4 and C-7. Dichloro-dioxepans IVa and IVb exhibited NMR signals at 3.4—4.3 ppm for protons on C-4 and C-7 as a broad unresolved multiplet due to rapid conformational exchanges of twist-boat structures[7]. The structures of IVa, IVb as well as IVc were proved by an alternate synthesis effected by addition of chlorine to dioxepins IIa—IIc.

Nitro-nitroso-dioxepane VI was isolated as an insoluble colourless solid[8] in 0.7—2.8% yield from the reaction mixture of IIb with nitryl chloride in light petroleum, or ether as a solvent.

Extension of the reaction conditions of dioxepins IIa and IIb with nitryl chloride to acetonitrile as a solvent resulted in the formation of 5-acetylamino-6-chloro-dioxepans VIIa and VIIb (after treating the reaction mixture with aqueous sodium hydrogen carbonate). In addition, some other nitriles were used to give acylamino-chloro-dioxepans VIIc—VIIe. The results are summarized in Table I. The formation of VII was explained in terms of nucleophylic attack by nitrile on a chloronium ion intermediate leading to a nitrilium ion followed by addition of base (OH^-)[9].



VII a $R_1=R_2=H$, $R_3=Me$
b $R_1=H$, $R_2=$iso-Pr, $R_3=Me$
c $R_1=R_2=H$, $R_3=Pr$
d $R_1=H$, $R_2=$iso-Pr, $R_3=Pr$
e $R_1=H$, $R_2=$iso-Pr, $R_3=CH_2Ph$

As expected, hydrodechlorination of chloro-nitro-dioxepans IIIa and IIIb proceeded easily in ether in the presence of triethylamine at 0—30 °C (anhydrous sodium acetate had no effect). Nitro-dioxepins Ia and Ib were obtained in 93 and 83% yields. The IR spectra of Ia and Ib exhibited characteristic absorptions of the nitro group on the unsaturated carbon at 1520 and 1335 cm^{-1}, respectively. The vinylic proton of Ia and Ib in the NMR spectrum appeared as a triplet at 7.3 ppm, while the protons on C-4 and C-7 appeared as two double multiplets at 4.4 and 4.8 ppm, respectively.

TABLE I

Physical and Analytical Data for 6-Acylamino-5-chlorodioxepans (VII)

Comp.	Nitrile	Yield/%	M. p.[a]/°C	Formula (M. w.)	Anal. calc'd found C/%	N/%	C/%	Principal Common IR bands NH asoc.	C=O (cm^{-1})
VIIa	MeCN	17.8	138—9	$C_7H_{12}ClNO_3$ (179.4)	43.42 43.31	6.25 6.13	7.23 7.55	3280	1660
VIIb	MeCN	23.5	166—7	$C_{10}H_{18}ClNO_3$ (235.4)	50.95 51.18	7.70 7.70	5.94 5.93	3270	1650
VIIc	PrCN	19.8	125—6	$C_9H_{16}ClNO_3$ (221.4)	48.76 49.00	7.28 7.49	6.32 6.55	3260	1645
VIId	PrCN	24.1	143—4	$C_{12}H_{22}ClNO_3$ (263.40)	54.64 54.38	8.41 8.66	5.51 5.58	3270	1645
VIIe	$C_6H_5CH_2CN$	5.7	151—2	$C_{16}H_{22}ClNO_3$ (311.40)	61.63 61.87	7.11 7.37	4.49 4.70	3260	1645

[a] Recrystallysed from the mixture benzene — chloroform 1 : 1

EXPERIMENTAL

Melting points (uncorrected) were determined on a Büchi apparatus. The UV spectra were taken on an Unicam SP-800 spectrometer, and IR spectra on a Perkin Elmer 257 instrument. ^1H NMR spectra were recorded on a Varian A-60 instrument (tetramethylsilane as internal standard). GLC was carried out with Perkin Elmer F-30 chromatograph equipped with a flame ionisation detector.

Purification of Nitryl Chloride

Nitryl chloride was prepared according to Shechter et. al.[1], liquified at — 25 °C, bubbled with dry nitrogen for ten minutes and used immediately.

Reaction of 4,7-Dihydro-1,3-dioxepine (IIa) with Nitryl Chloride

To a solution of nitryl chloride (10.6 g, 0.13 mol) in chloroform (50 ml), dioxepine[10] (IIa) (11.0 g, 0.11 mol) was added at 25—30 °C for 30 min and stirred for one hour. The mixture was then washed with water and aqueous sodium hydrogen carbonate. Chloroform was removed and the residue (17.4 g) fractionated in vacuo at 17 Torr* to give two fractions. The former with b. p. 78—82 °C (6.8 g, 35.8%) gave on redestillation 5,6-dichloro-1,3-dioxepane (IVa), b. p. 82—84 °C, 17 Torr (lit.[11] 56 °C,

* 1 Torr = 133.322 Pa

1 Torr); IR (film) 2795 (O—CH_2—O) and 1115 cm^{-1} (C—O—C); ^1H NMR (CCl_4) 3.4—4.2 (6H, m, 4,7-CH_2 and 5,6-CH) and 4.7 (2H, s, 2-CH_2) ppm.

The second fraction with b. p. 118—126 °C (5.0 g) solidified partially on standing. The solid part was filtered off (1.36 g, 6.8%) and recrystallised from light petroleum to give pure 5-chloro-6-nitro-1,3-dioxepane (IIIa), m. p. 36—37 °C, UV λ_{max} (MeOH) 216 nm (log ε 3.29); IR (KBr) 1550 and 1350 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) 3.9—4.4 (4H, m) and 4.7 (2H, m) (protons of 4,7-CH_2 and 5,6-CH) and 4.7 ppm (2H, s, 2-CH_2)

Anal. $C_5H_8ClNO_4$ (181.57) calc'd.: C 33.07; H 4.44; N 7.71%
found: C 33.32; H 4.57; N 7.98%

The oily residue after the separation of IIIa (3.64 g) was shown (GLC) to be a mixture of IIIa (78%), Ia (10%) and unknown (12%).

Reaction of 4,7-Dihydro-2-isopropyl-1,3-dioxepine (IIb) with Nitryl Chloride

To a solution of nitryl chloride (11.0 g, 0.14 mol) in light petroleum (50 ml) dioxepine (IIb)[10] (16.3 g, 0.11 mol) in light petroleum (20 ml) was added at 25—30 °C for 30 min and stirred for one hour. The insoluble product was collected, washed with ether and recrystallysed from acetonitrile to give 0.6 g (2.5%) 5-nitro-6-nitroso-1,3-dioxepane (VI), m. p. 130—131 °C. UV λ_{max} (acetonitrile) 205 nm (log ε 3.58) and 291 nm (log ε 3.43); IR (KBr) 1555, 1355 (NO_2) 1210 (NO), and 1135 cm^{-1} (C—O—C); ^1H NMR ($CDCl_3$) 0.9 (6H, d, *iso*-Pr-CH_3), 3.8—4.8 (5H, m, 4,7-CH_2 and 2-CH), 5.2 (1H, m) and 6.0 ppm (1H, m) (5-CH and 6-CH).

Anal. $C_8H_{14}N_2O_5$ (218.21) calc'd.: C 44.03; H 6.47; N 12.84%
found: C 44.11; H 6.71; N 12.62%

The mother liquid was washed with water and aqueous sodium hydrogen carbonate, dried and the solvent removed. The residue (15.3 g) was fractionated in vacuo at 0.35 Torr to give two fractions. The fraction with b. p. 48—66 °C gave on redestillation 5.4 g (23%) 5,6-dichloro-2-isopropyl-1,3-dioxepane (IVb), b. p. 66 °C 0.4 Torr; IR (film) 1115 cm^{-1} (C—O—C); ^1H NMR (CCl_4) 0.9 (6H, d, *iso*-Pr-CH_3), 1.8 (1H, m, *iso*-Pr-CH), 3.6—4.1 (6H, m, 4,7-CH_2 and 5,6-CH) and 4.3 ppm (1H, d, 2-CH).

Anal. $C_8H_{14}Cl_2O_2$ (213.1) calc'd.: C 45.08; H 6.22%
found: C 45.20; H 6.40%

On redestillation the second fraction with b. p. 76—86 °C (7.5 g) gave 6.1 g (24.8%) 5-chloro-6-nitro-2-isopropyl-1,3-dioxepane (IIIb), b. p. 81—82 °C 0.5 Torr; IR (film) 1550 and 1345 cm^{-1} (NO_2); ^1H NMR (CCl_4) 0.9 (6H, d, *iso*-Pr-CH_3), 1.8 (1H, m, *iso*-Pr-CH), 3.6—4.6 (6H, broad multiplet, 4,7-CH_2 and 5,6-CH), 4.2 ppm (1H, d, 2-CH).

2-Isopropyl-5-nitro-6-phenylamino-1,3-dioxepane (V)

A mixture of chloro-nitro-dioxepane IIIb (1 g, 0.0045 mol), acetonitrile (2 ml) and aniline (0.8 ml) was stirred at 60 °C for 2 h. The insolouble salt was separated, and the filtrate evaporated in vacuo to give crude V (0.95 g) after washing with light petroleum, m. p. 112—114 °C (recryst. from ethanol: m. p. 116 °C); UV (methanol) 209 nm (log ε 3.79), 242 nm (log ε 4.22) and 290 nm (log ε 3.42); IR (KBr) 3385 (NH), 3040 (=CH), 1602 (C=C arom.), 1540 and 1358 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) 1.0 (6H, dd, *iso*-Pr-CH_3), 1.8 (1H, m, *iso*-Pr-CH), 4.0—4.8 (8H, m, 4,7-CH_2, 5,6-CH, 2-CH and NH), 6.6—7.5 ppm (5H, m, aromatic protons).

Anal. $C_{14}H_{20}N_2O_4$ (280.32) calc'd.: C 59.98; H 7.19; N 9.99%
found: C 60.22; H 7.14; N 10.18%

4,7-Dihydro-5-nitro-1,3-dioxepin (Ia)

To a solution of IIIa (0.82 g, 0.0045 mol) in ether (50 ml), triethylamine (0.45 g, 0.0045 mol) was added at 10 °C and the mixture stirred for 10 min. After washing with water and drying ($MgSO_4$) ether was evaporated and the residue solid recrystallised to give 0.6 g (93%) of Ia, m. p. 48—49 °C; UV (Methanol) 245 nm (log ε 3.84); IR (KBr) 3070 (=CH), 2790 (O—CH_2—O), 1670 (C=C), 1520 and 1338 cm^{-1} (=C—NO_2); ^1H NMR ($CDCl_3$) 4.4 (2H, m, 4-CH_2), 4.8 (2H, m, 7-CH_2), 4.9 (2H, s, 2-CH_2) and 7.2 ppm (1H, t, 5-CH).

Anal. $C_5H_7NO_4$ (145.11) calc'd.: C 41.38; H 4.86; N 9.65%
found.: C 41.66; H 4.63; N 9.84%

4,7-Dihydro-2-isopropyl-5-nitro-1,3-dioxepin (Ib)

Hydrodechlorination of IIIb (1 g, 0.0045 mol) as described for IIIa gave 0.7 g (83.6%) of Ib, b. p. 90 °C at 1 Torr.; UV (methanol) 245 nm (log ε 3.71); IR (film) 3070 (=CH), 1675 (C=C), 1520 and 1335 cm^{-1} (=C—NO_2); ^1H NMR (CCl_4) 0.9 (6H, d, *iso*-Pr-CH_3, 1.9 (1H, m, *iso*-Pr-CH), 4.2—4.5 (3H, m, 7-CH_2 and 2-CH), 4.7 (2H, m, 4-CH_2), and 7.2 ppm (1H, t, 6-CH).

Anal. $C_8H_{13}NO_4$ (187.18) calc'd.: C 51.33; H 7.00; N 7.48%
found: C 51.21; H 7.13; N 7.73%

Reaction of 7,12-Dioxaspiro(5,6)-dodeca-9-ene (IIc) with Nitryl Chloride

To a solution of nitryl chloride (11.7 g, 0.14 mol) in chloroform (50 ml) dioxepine IIc[10] (20.5 g, 0.12 mol) in chloroform (20 ml) was added at 18—22 °C for 30 min and stirred for 1 h. The dark oil (21.4 g), obtained in the way as described for the reaction of IIa and IIb with nitryl chloryde, was fractionated in vacuo (0.65 Torr) to give 0.6 g of an unidentified mixture (b. p. 54—70 °C) and 8.4 g (b. p. 78—86 °C) of 9,10-dichloro-7,12-dioxaspiro(5,6)-dodecane (IVc). On redistillation, pure IVc was obtained with b. p. 82—85 °C at 0.3 Torr; IR (film) 1105 cm^{-1} (C—O—C); ^1H NMR (CCl_4) 1.5 (10H, s, $(CH_2)_5$) 3.8 (6H, s, 8,11-CH_2 and 9,10-CH).

Anal. $C_{10}H_{16}Cl_2O_2$ (239.14) calc'd.: C 50.22; H 6.74; Cl 29.64%
found: C 50.22; H 6.75; Cl 29.40%

Chlorination of Dioxepins IIa-c with Chlorine

General procedure: Chlorine was bubbled into a solution of dioxepine II (0.1 mol) in an apropriate solvent (200 ml) at —40 to —25 °C during 2 h. After washing with 10% aqueous sodium bisulfite and drying, the solvent was evaporated and the residue distilled in vacuo. Dichloro-dioxepane IVa was obtained in 35% yield (chloroform as a solvent), b. p. 85—88 °C at 19 Torr, dichloro-dioxepane IVb in 60% yield (dichloromethane as solvent) b. p. 62—66 °C at 0.3 Torr, and dichloro-dioxepane IVc in 41.8% yield (chloroform as a solvent) b. p. 80—85 °C at 0.3 Torr.

Reaction of Dioxepins IIa and IIb with Nitryl Chloride in Nitriles

General procedure: Dioxepine II (0.083 mol) was added dropwisse for 30 min to a solution of nitryl chloride (0.1 mol) in nitrile (50 ml) at 18—22 °C and stirred for additional 60 min. On neutralisation with aqueous sodium hydrogen carbonate, crude 6-acylamino-5-chloro-dioxepane VII separated as an insolouble solid (nitriles, yields, m. p. s., analyses, and IR are given in Table I).

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SAŽETAK

Kemija 1,3-dioksepina. I. Reakcija 4,7-dihidro-1,3-dioksepina s nitril kloridom

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Reakcijom 4,7-dihidro-1,3-dioksepina(II) s nitrilkloridom u kloroformu ili petroleteru dobivena je smjesa 5-klor-6-nitro-1,3-dioksepana(III) i 5,6-diklor-dioksepana (IV).Reakcijom u alkinitrilima dobiveni su i odgovarajući 6-acilamino-5-kloro-dioksepani(VII). Hidrodekloriranjem(III) u prisutnosti trietilamina pripravljeni su 5-nitro-4,7-dihidro-1,3-dioksepini(I).

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