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Preparation of 1,4-Cycloalkanediones by Hypoiodite Oxidation of Cycloalkanols

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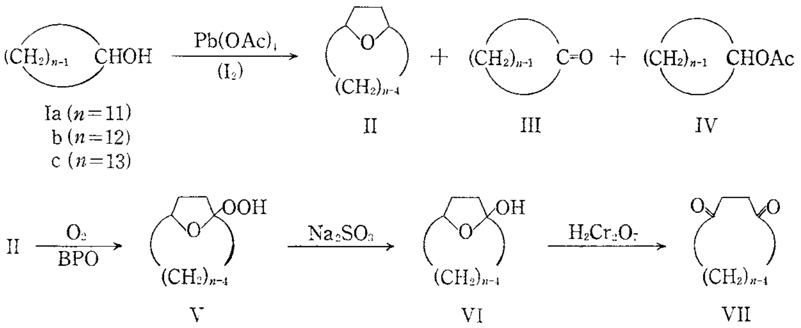
Lead tetraacetate oxidation of 11, 12 and 13-membered cycloalkanols gives improved yields of 2,5-polymethylenetetrahydrofurans II in the presence of iodine. Oxidative cleavage of II furnishes 1,4-cycloalkanediones VII.

Synthesis of [8](2,5)heterocyclophanes recently recorded involves the Paal-Knorr reaction of 1,4-cyclododecanedione (VIIb).[1] A new route has been found for an effective method of preparing homologous 1,4-diketones.*[1] This consists of oxidative ring closure of cycloalkanols I to 2,5-polymethylenetetrahydrofurans II and oxidative ring reopening of II into diketones VII.

While this work was in progress, Mihailovic *et al.*[6] reported lead tetraacetate oxidation of 6, 7, 8, 10, 12 and 16-membered cycloalkanols, which yielded cycloalkanones III and cycloalkyl acetates IV as main products. Bicyclic ethers of unknown structures were obtained in the oxidation of large ring alcohols. Tetrahydrofurans II are obtained in improved yields by the synergism of iodine (hypoiodite oxidation[7]). In the absence of iodine the main products were III and IV as recorded by



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*[1] Simple 1,4-cycloalkanediones hitherto recorded are 6,[2] 7,[3] 8,[4] and 12[5]-membered ones.

1) H. Nozaki, T. Koyama, T. Mori and R. Noyori, *Tetrahedron Lett.*, **1968**, 2128.

2) W. von Doering and A. A. R. Sayigh, *J. Org. Chem.*, **26**, 1365 (1961).

3) J. Rigaudy and P. Courtot, *C. R. Acad. Sci., Paris, Ser. C*, **248**, 3016 (1959).

4) A. C. Cope, S. W. Fenton and C. F. Spencer, *J. Amer. Chem. Soc.*, **74**, 5884 (1952).

5) B. Camerino and B. Patelli, *Experientia*, **20**, 260 (1964).

6) M. Lj. Mihailovic, Z. Cekovic, V. Andrevic, R. Matic and D. Jerevic, *Tetrahedron*, **24**, 4947 (1968).

7) K. Heusler and J. Kalvoda, *Angew. Chem. Int. Ed., Engl.*, **3**, 525 (1964).

Table 1. Reaction conditions and product yields in oxidation of cycloalkanols Ia—c

Substrate	Oxidant(s)	I : Oxidant(s) mole ratio	Solvent	Recovery of I (%)	Yield of product (%)$^{a)}$ II	III	IV
Ib	$Pb(OAc)_4$	1 : 1.2	PhH	8	$8^{b)}$	16	$32^{c)}$
Ib	$Pb(OAc)_4$, I_2	1 : 2.0 : 0.7	PhH	0	12	9	0
Ib	$Pb(OAc)_4$, I_2	1 : 2.0 : 0.5	$C_6H_{12}{}^{d)}$	34	18	2	0
Ib	$Pb(OAc)_4$, I_2	1 : 2.0 : 0.9	C_6H_{12}	0	27	3	0
Ib	$Pb(OAc)_4$, I_2	1 : 2.0 : 0.7	C_6H_{12}	2	37	8	0
Ia	$Pb(OAc)_4$	1 : 1.2	PhH	24	2	26	$15^{c)}$
Ia	$Pb(OAc)_4$, I_2	1 : 2.0 : 0.7	C_6H_{12}	1	$23^{e)}$	14	$0^{f)}$
Ic	$Pb(OAc)_4$	1 : 1.2	PhH	11	21	10	trace$^{c)}$
Ic	$Pb(OAc)_4$, I_2	1 : 2.0 : 0.7	C_6H_{12}	0	$38^{e)}$	2	0

a) The yields were determined from peak areas of GLC. In all experiments unidentified products were detected to the amount of 1—5% of all volatile products.
b) TLC of IIb showed one main and two minor spots.
c) A trace of cycloalkene was detected.
d) C_6H_{12} refers to cyclohexane.
e) TLC of IIa and IIc showed single spot.
f) 2,6-Hexamethylenetetrahydropyran was formed in an 11% yield.

Mihailovic.[6] The results are summarized in Table 1.

The yields were determined by gas liquid chromatography (GLC) and separation was effected by column chromatography. The best yields of II were obtained by hypoiodite oxidation conducted in cyclohexane at reflux temperature with lead tetraacetate and iodine in a mole ratio of 1 (alcohol) : 2.0 : 0.7. Although some workers successfully performed hypoiodite oxidation in benzene solution,[8] the present substrates failed to afford satisfactory results in benzene solvent. On careful thin layer chromatographic (TLC) analyses, ethers IIa and IIc showed single spot but IIb three spots as indicated. Following oxidative ring opening established them to be *cis* and/or *trans* tetrahydrofurans (mainly in the case of IIb). Each component was not characterized. The by-products III and IV were identified by comparison with authentic samples. Oxidation of Ia gave low yields of IIa, the byproduct being probably tetrahydropyran derivative (see experimental) formed in an 11% yield.

The effect of iodine is thus characterized by the increase of II at the expense of III and IV. This can be explained by assuming fast decomposition of the intermediate, $>$CHOPb(OAc)$_3$,[9] otherwise leading to III or IV, and/or by the consumption of lead tetraacetate through reaction with iodine.[10]

The cleavage of ether bond of II was attempted in several ways. Bromine in acetate-buffer, a reagent for oxidative cleavage of ethers recently reported,[11] did not react possibly due to the sparing solubility of II. *p*-Toluenesulfonyl acetate[12] or boron trifluoride in acetic anhydride[13] failed to give satisfactory results due to the formation of olefinic products. Hydroiodic acid afforded the desired 1,4-diiodocyclododecane, but transformation into 1,4-diketone proceeded sluggishly and the formation of olefinic products was again observed.

Finally the cleavage was carried out with success by means of autoxidation. The resulting hydroperoxides V were reduced to hemiketals VI. Chromic acid oxidation of VI afforded 1,4-diketones VII in 45—51% overall yields based on II. Among the 1,4-diketones, the 12-membered VIIb was identified by comparison with authentic sample.[5] The structures of other diketones were ascertained by elemental analyses, IR spectra and most convincingly by NMR spectra. The NMR spectra of VII showed a singlet (4H) at δ 2.62—2.65 (two methylenes between two carbonyl groups) and a diffused triplet (4H) at δ 2.35—2.40 (other α-methylenes).

The hypoiodite oxidation was applied to VIII in order to prepare a 1,4-diketone having one carbonyl group in side chain. The main product was, however, cycloundecyl acetate arising from so called "β-fragmentation,"[14] and tetrahydrafuran

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[8] J. F. Bagli, P. F. Morand and R. Gaudry, *J. Org. Chem.*, **28**, 1207 (1963).

[9] M. Lj. Mihailovic, Z. Cekovic, Z. Macsimovic, D. Jeremic, A. Milovanovic and Lj. Lorenc, *Tetrahedron*, **21**, 1395 (1965).

[10] C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, *Helv. Chim. Acta*, **45**, 1317 (1962).

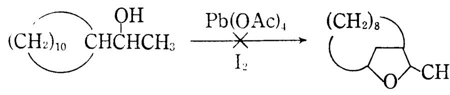
[11] N. C. Deno and N. H. Potter, *J. Amer. Chem. Soc.*, **89**, 3550 (1967).

[12] M. H. Karger and Y. Mazur, *ibid.*, **90**, 3878 (1968).

[13] W. H. W. Lunn, W. D. Podmore and S. S. Szinai, *J. Chem. Soc.*, *C*, **1968**, 1657.

[14] M. Lj. Mihailovic, M. Jakovljevic, V. Trifunovic, R. Vukov and Z. Cekovic, *Tetrahedron*, **24**, 6959 (1968).

IX was not obtained.



VIII IX

Experimental

All temperatures are uncorrected. NMR spectra were obtained on a JEOL C-60-H spectrometer in CCl_4 solutions with tetramethylsilane as an internal reference. Chemical shifts are given in ppm from this reference with the multiplicity of signals indicated in an abbreviated form. Mass spectra (MS) were measured on a Hitachi RMU 6C spectrometer at electrode voltage 70 eV. GLC was performed on HVSG or SE 30 on Chromosorb W with hydrogen as a carrier gas. TLC was conducted on Silica-gel G with *n*-hexane or benzene as a developing solvent.

Lead Tetraacetate Oxidation of Cycloalkanols (Ia—c). A mixture of $Pb(OAc)_4$ (6.2 g, 14 mmol), $CaCO_3$ (1.6 g, 16 mmol) and anhydrous benzene (40 m*l*) was heated at reflux for 15 min with stirring under nitrogen atmosphere. After cooling, cycloalkanol (I) (12 mmol) was added to the mixture and the whole was heated at reflux for 20 hr with vigorous stirring. The reaction mixture was cooled and inorganic substances were separated by filtration and washed with benzene. The filtrate and washings were combined, washed with aqueous KI, aqueous $Na_2S_2O_3$ and then with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was subjected to TLC and GLC analyses. Products III and IV were identified by comparison of their R_f values and retention times with those of authentic samples. The yields were determined from peak areas of GLC as summarized in Table 1. Isolation of bicyclic ethers II was difficult due to their low yields and was performed in the hypoiodite oxidation experiments.

Hypoiodite Oxidation of Cycloalkanols (Ia—c). A mixture of $Pb(OAc)_4$ (26.6 g, 60 mmol), $CaCO_3$ (9.0 g, 90 mmol) and cyclohexane (450 m*l*) was heated at reflux for 15 min with stirring under nitrogen atmosphere, cooled and added with cycloalkanol (I) (30 mmol) and I_2 (5.3 g, 21 mmol). Heating and stirring were continued for 2 hr. After cooling, the inorganic substances were filtered and washed with cyclohexane. The combined cyclohexane solution was washed with aqueous $Na_2S_2O_3$ and then with water, dried (Na_2SO_4), and concentrated *in vacuo*. The residual oil was subjected to TLC and GLC, and the yields were calculated from peak areas of GLC (see Table 1). Oxidation of Ia gave a mixture of bicyclic ethers, whose separation was effected by column chromatography on alumina with *n*-hexane as an eluant. Work up of less adsorbed fractions afforded 12-oxabicyclo[7.2.1]dodecane (IIa), which formed a colorless oil, bp 93—96°C/4 mmHg. IR (cm^{-1}, neat): 1090, 1042 (C–O–C). NMR (δ): 4.25—3.80 (m, 2H), 2.20—1.15 (m, 18H). Found: C, 78.7; H, 11.9%. Calcd for $C_{11}H_{20}O$: C, 78.5; H, 12.0%. MS: parent peak at *m*/*e* 168.

Work up of more adsorbed fractions afforded a colorless oil, bp 93—95°C/3 mmHg. IR (cm^{-1}, neat): 1100, 1048 (C–O–C). NMR (δ): 3.98—3.50 (m,2H), 2.33—0.75 (m, 18H). Found: C, 78.7; H, 11.9%. Calcd for $C_{11}H_{20}O$: C, 78.5; H, 12.0%. MS: parent peak at *m*/*e* 168. Oxidative cleavage of this bicyclic ether conducted similarly as mentioned below for the preparation of 1,4-diketones from II gave an oily diketone, bp 100—105°C/2 mmHg. IR (cm^{-1}, neat): 1705 (C=O). NMR (δ); 2.70—2.00 (m, 8H), 2.00—0.90 (m, 10H). Found: C, 72.3; H, 9.9%. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0%. These data indicate that this ether is not epoxide, oxetane or tetrahydrofuran. The most likely structure should be a tetrahydropyran or 12-oxabicyclo[6.3.1]dodecane. Further information was not obtained due to lack of material.

Oxidation of Ib and work up gave IIb as a colorless oil, bp 97—100°C/3 mmHg. IR (cm^{-1}, neat): 1091, 1055 (C–O–C). NMR (δ): 4.20—3.70 (m, 2H), 2.10—0.75 (m, 20H). Found: C, 79.6; H, 12.2%. Calcd for $C_{12}H_{22}O$: C, 79.1; H, 12.2%. MS: parent peak at *m*/*e* 182.

Oxidation of Ic and work up gave IIc as a colorless oil, bp 110—114°C/5 mmHg. IR (cm^{-1}, neat): 1085, 1060 (C–O–C). NMR (δ): 4.00—3.50 (m, 2H), 2.05—0.85 (m, 22H). Found: C, 79.7; H, 12.5%. Calcd for $C_{13}H_{24}O$: C, 79.5; H, 12.3%. MS: parent peak at *m*/*e* 196.

Oxidative Cleavage of Bicyclic Ethers (IIa—c). Oxygen was bubbled at a rate of *ca.* 10 m*l*/min for 20 hr into a mixture of II (8.8 mmol) and benzoyl peroxide (20 mg) heated at 85—90°C. The resulting highly viscous oil was taken up in ether (100 m*l*), washed with aqueous Na_2SO_3 and then with water, and concentrated into about 20 m*l*. This ethereal solution was added with a mixture of $Na_2Cr_2O_7 \cdot 2H_2O$ (2.0 g, 6.7 mmol), concd. H_2SO_4 (2.5 m*l*) and water (10 m*l*), and the whole was stirred for 15 hr at room temperature. The ethereal layer was washed with aqueous $NaHCO_3$ and then with water, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residual oil by silica-gel column chromatography with benzene as an eluant afforded the desired diketone VII as a colorless solid or oil.

Oxidation of IIa gave 1,4-cycloundecanedione (VIIa) as a colorless solid, mp 64—65°C (from *n*-hexane), in a 45% yield. IR (cm^{-1}, Nujol): 1703 (C=O). NMR (δ): 2.63 (s, 4H), 2.35 (diffused t, 4H), 1.90—1.05 (m, 10H). Found: C, 72.4; H, 10.0%. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0%.

Oxidation of IIb gave 1,4-cyclododecanedione (VIIb) as a colorless solid, mp and mixed mp 78—79°C (from petroleum ether), in a 49% yield. IR spectrum was superimposable with that of authentic specimen.[5] NMR (δ): 2.65 (s, 4H), 2.38 (diffused t, 4H), 1.85—0.95 (m, 12H).

Oxidation of IIc gave 1,4-cyclotridecanedione (VIIc) as a colorless oil, bp 110—113°C/2 mmHg, in a 51% yield. IR (cm^{-1}, neat): 1705 (C=O). NMR (δ): 2.26 (s, 4H), 2.40 (diffused t, 4H), 1.85—0.95 (m, 14H). Found: C, 74.4; H, 10.6%. Calcd for $C_{13}H_{22}O_2$: C, 74.2; H, 10.5%.

Cycloundecylmethylcarbinol (VIII). This alcohol was prepared from cycloundecanecarboxylic acid[15] through MeLi treatment[16] and $LiAlH_4$ reduction in a

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[15] W. Ziegenbein, *Chem. Ber.*, **94**, 2989 (1961).

[16] C. H. DePuy, G. M. Dappen, K. L. Eilers and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

66% yield. The product formed an oil, bp 132—133°C/7 mmHg. IR (cm^{-1}, neat): 3370 (OH), 1370 (CH_3). NMR (δ): 3.70—3.27 (m, 1H), 2.37 (broad s, 1H), 1.80—1.20 (m, 21H), 1.09 (d, 3H). Found: C, 78.5; H, 13.5%. Calcd for $C_{13}H_{26}O$: C, 78.7; H, 13.2%.

Hypoiodite Oxidation of VIII. Oxidation was performed in a similar way as mentioned above and the resulting mixture was subjected to TLC and GLC analyses. The main product was cycloundecyl acetate (IVa) isolated in a 29% yield, which was identified by comparison with authentic sample. A trace of unidentified product was detected. No evidence was obtained in support of formation of tetrahydrofuran IX.

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