Table II. Tetrahydro-4-pyrone Ketals of Nucleosides

Nucleoside derivative	Mp, °C	Yield, %[a]	$[\alpha]^{28}D$, deg[b]	$t_{1/2}$, min[c]
Uridine 2′-ketal (V)	167–169	61	−15.7	24
Thymidine 5′-ketal	169–171	85	+9.7	10.5
Uridine 2′,5′-bisketal[d] (VIa, B = uracil-1)		51	+2.4	9.5[e]
Adenosine 2′,5′-bisketal (VIa, B = adenine-9)	183–184	52	−50	

[a] Based on two steps from 3′-O-acetyl or 3′,5′-di-O-acetyl nucleoside. [b] At suitable concentrations, in ethanol solution. [c] At 20° in 0.01 *N* hydrochloric acid. [d] Obtained as a glass in quantitative yield from its crystalline 3′-O-acetate (VIb, B = uracil-1; mp 102–104°). [e] For conversion of starting material into a mixture of 2′- and 5′-monoketals.

duced to crystallize, the corresponding adenosine derivative VIa (B = adenine-9) has been isolated as a crystalline solid in 52% over-all yield (see Table II).

Thus the tetrahydro-4-pyrone ketal system (methoxytetrahydropyranyl group) appears to be most suitable for the protection of alcoholic hydroxyl functions in oligoribonucleotide synthesis; it has the required acid lability, and its use leads to satisfactory yields of pure crystalline mono- and diprotected ribonucleoside derivatives. This symmetrical ketal system should prove to be a useful alternative to the tetrahydropyranyl protecting group in other branches of natural product chemistry.

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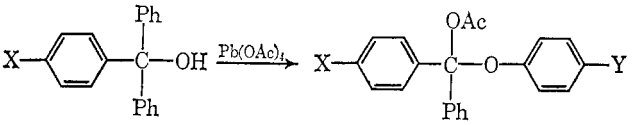
Received April 25, 1967

Mechanism of the Oxidation of Monohydric Alcohols with Lead Tetraacetate. Rearrangement in the Triarylmethanol Series

Sir:

In recent years the ability of lead tetraacetate to oxidize monohydric alcohols has been exploited extensively from the synthetic standpoint.[1] Many of the products formed in this versatile reaction can be accounted for in terms of a mechanism involving the initial production of alkoxy radicals.[1,2] However, other mechanisms have been considered,[1-3] and the evidence for radicals as prime intermediates has remained suggestive rather than conclusive. The present communication reports the discovery of a novel lead tetraacetate induced rearrangement whose investigation has yielded definitive information regarding the mechanism of the alcohol oxidation reaction.

Triphenylmethanol (**1a**) reacts with lead tetraacetate[4] in benzene, benzene–pyridine, or acetonitrile to form hemiketal ester **2a** in yields ranging up to 91%.[5] Although the hydrolytic instability of **2a** has prevented



1a, X = H
b, X = NO_2
c, X = OMe

2a, X = Y = H
b, X = H; Y = NO_2
c, X = NO_2; Y = H
d, X = H; Y = OMe
e, X = OMe; Y = H

its isolation, its presence has been conclusively established by infrared, nmr, and chemical ionization mass spectral measurements[6] on crude reaction products, and by the formation of benzophenone, dimethoxydiphenylmethane, methoxyphenoxydiphenylmethane, acetic acid, and phenol upon saponification of crude **2a** with potassium hydroxide in aqueous methanol.

Reactions of lead tetraacetate with **1b** or **1c** gave mixtures of hemiketal acetates **2b,c** or **2d,e**.[5] These mixtures were hydrolyzed, and relative migratory aptitudes for the substituted aryl groups were then calculated from the amounts of ketones and ketals thus obtained. In the case of **1b**, the lead tetraacetate reactions were run in benzene, benzene–pyridine, benzene–pyridine containing a soluble copper catalyst, acetonitrile, and acetonitrile containing cupric acetate.[4] Despite the wide variations in conditions and their attendant effects upon reaction rate, all of these experiments gave the same statistically corrected ratio for *p*-nitrophenyl:phenyl migration (within experimental error). Its value was 4.4 ± 0.3, a result which demands the operation of a homolytic mechanism.[7] Competitive occurrence of an ionic mechanism is ruled out by the insensitivity of the ratio to solvent polarity and the presence of copper salts or pyridine.[8] A concerted homolytic mechanism (see below) seems unlikely, since it would require a dependence of the ratio upon the nature of the leaving group.[9] Therefore, in this case it appears that the alkoxy radical corresponding to **1b** is the sole rearranging species.[10]

(1) For a review, see K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Ed. Engl.*, **3**, 525 (1964).

(2) See, *inter alia*, G. Cainelli, B. Kamber, J. Keller, M. L. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **44**, 518 (1961); M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. L. Mihailović, K. Schaffner, D. Arigoni, and O. Jeger, *ibid.*, **45**, 2674 (1962); K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *ibid.*, **46**, 352 (1963); D. Hauser, K. Schaffner, and O. Jeger, *ibid.*, **47**, 1883 (1964); D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner, and O. Jeger, *ibid.*, **47**, 1961 (1964); K. Heusler, *Tetrahedron Letters*, 3975 (1964); M. Stefanović, M. Gašić, L. Lorenc, and M. L. Mihailović, *Tetrahedron*, **20**, 2289 (1964); M. L. Mihailović, Z. Maksimović, D. Jeremić, Ž. Čeković, A. Milovanović, and L. Lorenc, *ibid.*, **21**, 1395 (1965); M. L. Mihailović, Ž. Čeković, Z. Maksimović, D. Jeremić, L. Lorenc, and R. I. Mamuzić, *ibid.*, **21**, 2799 (1965); M. L. Mihailović, Ž. Čeković, and D. Jeremić, *ibid.*, **21**, 2813 (1965); M. L. Mihailović and M. Miloradović, *ibid.*, **22**, 723 (1966); M. L. Mihailović, J. Bošnjak, Z. Maksimović, Ž. Čeković, and L. Lorenc, *ibid.*, **22**, 955 (1966); R. E. Partch, *J. Org. Chem.*, **30**, 2498 (1965).

(3) G. Cainelli, M. L. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959); W. A. Mosher and H. A. Neidig, *J. Am. Chem. Soc.*, **72**, 4452 (1950); W. A. Mosher, C. L. Kehr, and L. W. Wright, *J. Org. Chem.*, **26**, 1044 (1961); M. S. Kharasch, H. N. Friedlander, and W. H. Urry, *ibid.*, **16**, 533 (1951); S. Moon and J. M. Lodge, *ibid.*, **29**, 3453 (1964); R. Moriarty and K. Kapadia, *Tetrahedron Letters*, 1165 (1964).

(4) See footnotes to Table I for a summary of conditions,

(5) Side reactions also occur, but to a relatively minor extent.

(6) (a) Details will be presented in a later report. (b) For discussions of chemical ionization mass spectrometry, see M. S. B. Munson and F. H. Field, *J. Am. Chem. Soc.*, **88**, 2621, 4337 (1966).

(7) Compare (a) P. D. Bartlett and J. D. Cotman, Jr., *ibid.*, **72**, 3095 (1950); (b) W. Dilthey, F. Quint, and H. Dierichs, *J. Prakt. Chem.*, **151**, 25 (1938).

(8) (a) Copper salts strongly catalyze the decomposition of Pb(IV) esters *via* a radical chain mechanism. Thermal homolysis of these esters is also believed to be sensitized by complexation with pyridine. See J. K. Kochi, *J. Am. Chem. Soc.*, **87**, 3609 (1965); *J. Org. Chem.*, **30**, 3265 (1965). (b) Copper salt catalysis in the Pb(IV) oxidation of alcohols has recently been observed by other workers. See G. Cainelli and F. Minisci, *Chim. Ind.* (Milan), **47**, 1214 (1965); G. Cainelli and S. Morrocchi, *Atti Accad. Nazl. Lincei Rend. Classe Sci. Fis. Mat. Nat.*, **40**, 464, 591 (1966).

(9) The leaving group should be different in reactions with pyridine if complexation[8a] occurs.

(10) The degree of kinetic freedom associated with this radical is not specified.

Table I. Reactions of 1c with Lead Tetraacetate[a]

Solvent	Additives	Time, hr	Yield,[b] moles/mole of 1c p-MeO-(Ph)$_2$CO	(Ph)$_2$CO	Mig apt[c] p-MeO-Ph-:Ph-
PhH	...	95	0.218	0.370	3.4
PhH[d]	Py[e]	23	0.248	0.206	1.7
PhH	Cu[f]	22	0.343	0.203	1.2
PhH[d]	Py,[e] Cu[f]	1.5	0.162	0.0855	1.1
PhH	$PhNO_2$[g]	100	0.0934	0.570	12
MeCN	...	95	0.0883	0.578	13
MeCN	Py[h]	19	0.122	0.202	3.3
MeCN	Cu[i]	22	0.205	0.365	3.6
MeCN	Py,[h] Cu[i]	18	0.153	0.0977	1.3
MeCN	$PhNO_2$[j]	95	0.0590	0.464	16

[a] 1c, 3.27 mmoles; $Pb(OAc)_4$, 7.22 mmoles unless noted otherwise; solvent, 20 ml unless noted otherwise; $CaCO_3$, 15.0 mmoles (used only in experiments without pyridine); 82 ± 2°. Oxygen had no effect on results. [b] Analyses by glpc; yields of ketals included. [c] 2 [moles of (Ph)$_2$CO]/moles of p-MeO(Ph)$_2$CO. [d] 25 ml; $Pb(OAc)_4$, 9.83 mmoles. [e] Pyridine, 19.7 mmoles. [f] Harshaw "Uversol copper liquid 8%," equivalent to 1.00 g-atom of Cu. [g] 3.27 mmoles. [h] Pyridine, 14.5 mmoles. [i] $Cu(OAc)_2 \cdot H_2O$, 1.00 mmole. [j] 6.54 mmoles.

However, the alkoxy radical mechanism is not the only one through which the rearrangement can proceed. In the case of 1c, the occurrence of *two* mechanisms is clearly shown by the marked influence of reaction conditions upon the p-methoxyphenyl:phenyl migratory ratio (Table I). The low ratios obtained with pyridine and copper salts are believed to reflect the predominant operation of the alkoxy radical mechanism,[8,11] while the high values obtained in acetonitrile and the experiments using nitrobenzene are consistent with the preferential decomposition of a first-formed Pb(IV) alcoholate *via* a concerted, quasiionic[11] process (either heterolytic or homolytic) involving aryl participation. Our results suggest that the quasiionic mechanism is likely to be observed only in cases where neighboring groups bearing strongly electron-donating substituents are near the hydroxyl function.

Since nitrobenzene caused no marked increases in reaction rate or hemiketal ester yields, did not cause the formation of new products, failed to reduce the over-all material balance (based on 1c), and was not used in large enough concentration to affect medium polarity significantly, its effect upon the p-methoxyphenyl:phenyl ratio is apparently due to selective inhibition[6a] of a radical *chain* process rather than to selective acceleration of the quasiionic mode. A scheme which accounts for the available facts relating to the radical mechanism is shown below.[12]

Initiation

$$Ar_3COH + Pb(OAc)_4 \longrightarrow Ar_3COPb(OAc)_3 + HOAc$$

$$Ar_3COPb(OAc)_3 \longrightarrow Ar_3CO\cdot + (AcO)_3Pb\cdot$$

Propagation

$$Ar_3CO\cdot \longrightarrow Ar_2COAr$$

$$Ar_2COAr + Ar_3COPb(OAc)_3 \longrightarrow 2 + Ar_3COPb(OAc)_2$$

$$Ar_3COPb(OAc)_2 \longrightarrow Pb(OAc)_2 + Ar_3CO\cdot$$

Termination

$$Ar_2COAr + (AcO)_3Pb\cdot \longrightarrow 2 + Pb(OAc)_2$$

In view of the foregoing observations, the occurrence of radical chain mechanisms in the oxidation of other types of monohydric alcohols with lead tetraacetate seems highly probable.

Acknowledgment. The author is indebted to Mr. H. J. Tarski for valuable technical assistance and to Dr. F. H. Field for the chemical ionization mass spectra.

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Received April 7, 1967

New Syntheses of Alloxazines[1]

Sir:

Alloxazines and isoalloxazines[2] are customarily prepared by condensation of (a) an o-phenylenediamine with alloxan,[3] (b) a 4,5-diaminopyrimidine with an o-benzoquinone,[4] (c) an o-aminoazobenzene with a barbituric acid,[5] (d) a 5-nitrosopyrimidine with an aromatic amine[6] or an o-phenylenediamine,[7] or (e) by nitrosation of a 6-arylaminouracil.[8] We wish to report three new synthetic approaches to alloxazines which not only are applicable, in principle, to the preparation of other condensed pyrazine heterocycles, but which offer further versatility in the synthesis of alloxazines with different origins for N_5 and N_{10}.

Method A. Recent studies on the deoxygenation of aromatic nitro compounds by triethyl phosphite[9] support the intermediacy of nitrene intermediates. Capture of these nitrenes by intramolecular insertion has been utilized for the preparation of a number of heterocyclic systems (carbazoles,[10] benzotriazoles,[10] indazoles,[10] phenothiazines,[11] anthranils,[11] indoles,[10,12] pyrrolo[3,2-*d*]pyrimidines[13]). We report the first application of this procedure to the synthesis of a condensed pyrazine system. Thus, refluxing 1,3-di-

(1) This research was supported in part by Contract DA-49-193-MD-2777 from the Department of the Army, Walter Reed Army Medical Center, and in part by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

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(11) p-Methoxyphenyl:phenyl migratory ratios for alkoxy radical rearrangements have apparently not been reported previously. However, the groups are known to show comparable reactivities in the homolytic neophyl rearrangement [C. Rüchardt and R. Hecht, *Tetrahedron Letters*, 961 (1962)]. Ionic decompositions of p-methoxytriphenylmethyl hydroperoxide[7b] and the corresponding perbenzoate (I. J. Levine, Ph.D. Thesis, University of Kansas, 1960) give preferential p-methoxyphenyl migration.

(12) A similar scheme which does not involve Pb(III) species is also possible.