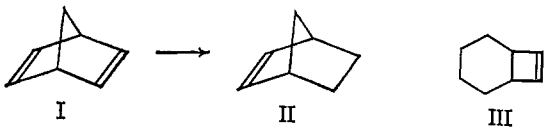
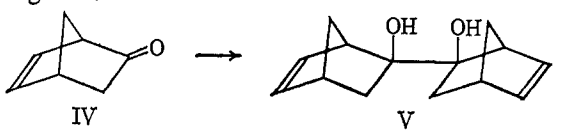
norbornane or nortricyclene in the product could be found.[4] To rule out the possibility that the difference in ease of reduction of I and II might be due to their difference in strain energy rather than to a double bond perturbation in I, a cyclobutene (III) was examined and found to be inert.



I II III

Norbornenone (IV, λ_{max} 301 mμ (ϵ 292)) was found to be reduced under these conditions to a mixture of diastereomeric pinacols (V).[7] Similar treatment of norbornanone (λ_{max} 287 mμ (ϵ 29)) gave only recovered starting material.

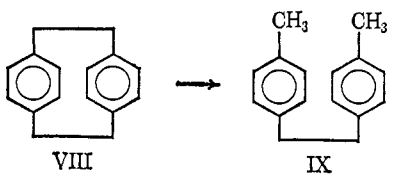


IV V

It is thus clear that the light absorption properties of a molecule, which reflect the difference between its ground- and excited-state energies, may be used qualitatively to predict the ease with which it can accept an electron in its lowest lying antibonding orbital. The energy of the excited molecule will obviously be different from that of the radical ion which is intermediate to the reduction product because the latter possesses one more electron.

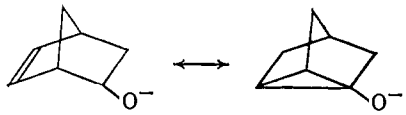
This correlation predicts that a number of other types of compound might also be reducible by metal–ammonia systems. 1-*t*-Butyl-3,3-dimethylcyclopropene (VI,[8] λ_{max} 195 mμ (ϵ 4400)) was examined and found to be reduced extremely rapidly to the corresponding cyclopropane[8] (VII, 85%). Similarly, [2.2]paracyclophane (VIII)[9] underwent reduction to di-*p*-tolylethane (IX, 100%) under conditions employed with other substrates.

VI VII



VIII IX

An intriguing question posed in the facile reductions of I and IV is whether or not nonclassical radical ions are involved. Particularly in the reduction of IV there can be little doubt that the intermediate X is extremely long-lived relative to typical nonconjugated radical ions. Repeated attempts[10] to obtain evidence for nonclassical behavior in the norbornenyl radical have failed, and it appears there is none. The radical ion in question here is electronically quite different, however, and its pronounced stability (long life) is suggestive of a nonclassical structure. An alternate



X

rationale based on steady-state concentration differences of radical ions cannot be dismissed (M + $e^- \rightleftarrows M\cdot^-$, k_1 being very different but k_{-1} being similar for norbornanone and norbornenone), but it is considered unlikely.

(3) "Isolated" double bonds are not reduced without an added proton source and even then only terminal double bonds are affected: H. Greenfield, R. A. Friedel, and M. Orchin, *J. Am. Chem. Soc.*, 76, 1258 (1954).

(4) The reduction of I to norbornane and nortricyclene with lithium in ethylamine (Benkeser conditions[5]) has been reported.[6] It should be noted that this technique is effective in reducing virtually all isolated double bonds.

(5) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, 28, 1094 (1963), and many references cited therein.

(6) J. G. Trayhnam, *ibid.*, 25, 833 (1960).

(7) The mixture (60%, mp 80–83°) was not separated but gave satisfactory nmr, infrared, and mass spectral data and analyzed correctly for $C_{14}H_{18}O_2$. Periodic acid cleaved it to norbornenone (83%).

(8) T. C. Shield and P. D. Gardner, manuscript in preparation.

(9) D. J. Cram, N. L. Allinger, and H. Steinberg, *J. Am. Chem. Soc.*, 76, 6132 (1954), describe the spectral properties of [2.2]paracyclophane. We are indebted to Professor Cram for a generous sample of this material.

(10) *Cf.* C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, 31, 3381 (1966), and references cited therein.

(11) National Science Foundation Predoctoral Fellow, 1962–1963.

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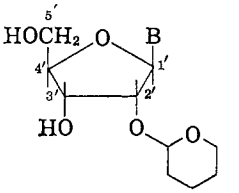
A Symmetrical Alternative to the Tetrahydropyranyl Protecting Group

Sir:

An obvious inherent disadvantage in the use of the tetrahydropyranyl group for the protection of optically active alcohols is that it leads to the introduction of an additional asymmetric carbon center (or centers), and thereby to mixtures of diastereoisomers being obtained.[1]



I

In connection with our work on oligoribonucleotide synthesis,[2] we undertook the preparation of a series of 2′-O-tetrahydropyranyl ribonucleosides (I) and obtained mixtures of diastereoisomers.[3] Although the latter could be separated and obtained crystalline,[4] the yield of pure isomer did not normally exceed 50%. However, after an unsuccessful attempt to isolate a pure crystalline 2′,5′-bis(tetrahydropyranyl) ribonucleoside derivative, the search for an alternative, symmetrical acid-labile protecting group become more urgent. Unlike other workers engaged in oligoribonucleotide synthesis,[5] we have concluded[3] that the tetrahydropy-

(1) C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951); A. N. de Belder, P. J. Garegg, B. Lindberg, G. Petropavlovskii, and O. Theander, *Acta Chem. Scand.*, 16, 623 (1962).

(2) B. E. Griffin and C. B. Reese, *Tetrahedron Letters*, 2925 (1964).

(3) B. E. Griffin, M. Jarman, and C. B. Reese, *Tetrahedron*, in press.

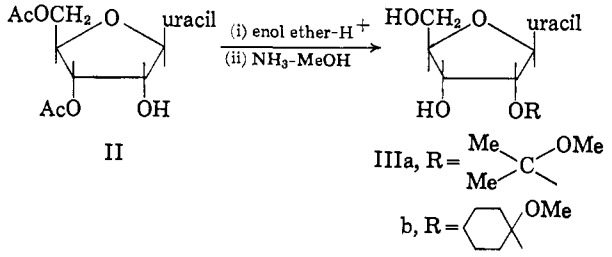
(4) As it is intended that the synthetic oligomers should contain only 3′→5′ internucleotidic linkages, it is a reasonable precaution to use only pure crystalline 2′-protected ribonucleoside derivatives (*e.g.*, I) as intermediates.

(5) D. H. Rammler and H. G. Khorana, *J. Am. Chem. Soc.*, 84, 3112 (1962); J. Smrt and S. Chládek, *Collection Czech. Chem. Commun.*,

ranyl acetal system has approximately optimal hydrolysis properties for an acid-labile protecting group: it may be removed under very mild conditions,[6] but is stable enough to allow protected oligomers to be purified.

Thus a satisfactory solution to this problem would be to find a symmetrical ketal system which underwent hydrolysis, in aqueous acid, at approximately the same rate as the tetrahydropyranyl group.[6] However, the best approach to such a solution was not immediately apparent as it had been reported[8] that simple ketals were over 10^3 times more labile than the corresponding acetals.[9]

Chart I



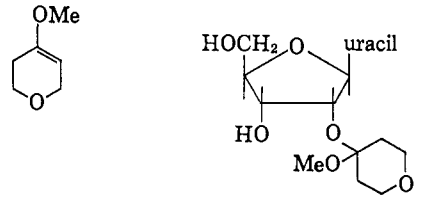
The 2′-acetone and cyclohexanone ketals of uridine (IIIa and IIIb) were prepared[10] from 3′,5′-di-O-acetyluridine[11] (II) and the appropriate enol ethers (2-methoxypropene[12] and 1-methoxycyclohexene,[13] respectively) by the procedure indicated in Chart I. The half-times of hydrolysis of these derivatives at 20° and pH 4 are given in Table I. As the rate of ketal hydrolysis[8] is proportional to $[H^+]$, $t_{1/2}$ for IIIa may be calculated to be 0.04 min at 20° and pH 2. As anticipated, this is less than $10^{-3} t_{1/2}$ for 2′-O-tetrahydropyranyluridine[6] under the same conditions. Surprisingly,[14] the cyclohexanone ketal IIIb is only 2.5 times more stable than IIIa.

Table I. Half-times ($t_{1/2}$) of Hydrolysis of Uridine 2′-Ketals (III)[a] in 0.1 *M* Aqueous Sodium Citrate (pH 4.0) at 20°

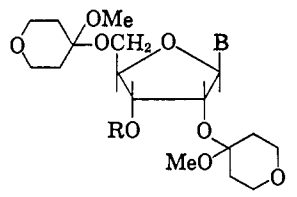
Compd	Yield, %[b]	Mp, °C	$t_{1/2}$, min
IIIa	42	185 dec	4[c]
IIIb	30	149–151	10

[a] 0.02 *M* solutions of nucleoside derivatives were used. [b] Represents over-all yield based on II. [c] $t_{1/2}$ for the corresponding 5′-protected uridine derivative was reported to be 1 min in 0.1 *M* acetate buffer (pH 4.7) at 25° (A. Hampton, *J. Am. Chem. Soc.*, **87**, 4654 (1965)).

It had been shown[8] that acetal and ketal systems could be stabilized to acidic hydrolysis by the introduction of electron-withdrawing groups. The idea that the inductive effect of a β-oxygen atom, if the latter were constrained in a ring system, might be sufficient for the present purpose was suggested by the fact that the pK_a of morpholine (8.70) was 2.52 units less than that of piperidine.[15] This indicates that a β-oxygen atom can destabilize a substituted ammonium ion by a factor of *ca.* 330. As the rate of ketal hydrolysis depends on the stability of the intermediate carbonium ion,[8] an estimate of $t_{1/2}$ = 33 min at pH 2 and 20° can be made for the hydrolysis of the uridine 2′-ketal of tetrahydro-4-pyrone (V) if the β-oxygen atom is assumed to exert an equivalent destabilizing effect on a carbonium ion.[16]



IV V



VIa, R=H
b, R=Ac

Reaction between 3′,5′-di-O-acetyluridine[11] (II) and and excess of 4-methoxy-5,6-dihydro-2H-pyran[17] (IV) in the presence of toluene-*p*-sulfonic acid followed by treatment with methanolic ammonia gave the required uridine 2′-ketal (V) as a crystalline solid, in 61% yield. As indicated in Table II, its acid lability ($t_{1/2}$ = 24 min at pH 2 and 20°) is remarkably close to the above estimate and is *ca.* three times as great as that of 2′-O-tetrahydropyranyluridine.[6] In the same way the corresponding thymidine 5′-ketal, a useful intermediate in oligodeoxyribonucleotide synthesis, was prepared from 3′-O-acetylthymidine in 85% over-all yield. It is noteworthy that the 5′-ketal is more acid labile than the 2′-ketal system (see Table II).

Reaction between 3′-O-acetyluridine[11] and the enol ether IV under the usual conditions gave the diprotected derivative VIb (R = uracil-1), isolated as a crystalline solid in over 50% yield. Although the product VIa (B = uracil-1), obtained by treating the latter with methanolic ammonia, has not yet been in-

31, 2978 (1966); F. Cramer, H.-J. Rhaese, S. Rittner, and K.-H. Scheit, *Ann.*, **683**, 199 (1965).

(6) At pH 2 (in 0.01 *N* hydrochloric acid solution) and 20°, the half-time ($t_{1/2}$) of hydrolysis of 2′-O-tetrahydropyranyluridine (I, B = uracil-1) is 80 min. Thus the tetrahydropyranyl group may be removed from a protected oligomer with a negligible amount of concomitant degradation and isomerization.[7]

(7) D. M. Brown, D. I. Magrath, A. H. Neilson, and A. R. Todd, *Nature*, **177**, 1124 (1956).

(8) M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **77**, 3146, 5590 (1955).

(9) The latter are, in turn, >10^3 times as labile as the corresponding formaldehyde acetals. Thus[8] the relative rates of hydrolysis of $CH_2(OEt)_2$, $MeCH(OEt)_2$, and $Me_2C(OEt)_2$ at 25° in dioxane–water are $1:6 \times 10^3:1.8 \times 10^7$.

(10) Satisfactory analytical data were obtained for all new compounds described.

(11) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2315 (1967).

(12) L. Claisen, *Chem. Ber.*, **31**, 1019 (1898).

(13) D. G. Lindsay and C. B. Reese, *Tetrahedron*, **21**, 1673 (1965).

(14) H. C. Brown, R. S. Fletcher, and R. B. Johannensen, *J. Am. Chem. Soc.*, **73**, 212 (1951).

(15) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen & Co. Ltd., London, 1962, p 141.

(16) The tetrahydro-4-pyrone ketal V is assumed to be 330 times more resistant to acidic hydrolysis than the cyclohexanone ketal IIIb. The latter would be expected to have $t_{1/2}$ = 0.1 min at pH 2 and 20° (see Table I).

(17) When 4,4-dimethoxytetrahydropyran [bp 64–66° (15 mm)], obtained from tetrahydro-4-pyrone[18] in 94% yield, was distilled with mesitylenesulfonic acid (0.1% by weight), 4-methoxy-5,6-dihydro-2H-pyran (IV) [bp 156–157° (760 mm)] was obtained in over 75% yield. In reactions with nucleoside derivatives, *ca.* 8 molecular equiv of IV was used per hydroxyl function to be protected.

(18) S. Olsen and R. Bredoch, *Chem. Ber.*, **91**, 1589 (1958).

Table II. Tetrahydro-4-pyrone Ketals of Nucleosides

Nucleoside derivative	Mp, °C	Yield, %[a]	$[\alpha]^{23}D$, 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.

(19) Holder of a Science Research Council Research Studentship.

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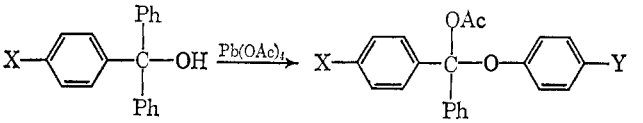
Received April 25, 1967

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.