${\vartriangle}^3$ -DIHYDROPYRANS AND TETRAHYDROPYRANS BY REDUCTION OF PYRYLIUM SALTS WITH SODIUM BOROHYDRIDE IN ACETIC ACID 1

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<u>Abstract</u>. The major reduction products with triacetoxyborohydride (NaBH, in AcOH) of 2,4,6--trisubstituted pyrylium salts bearing alkyl substituents in the 2- and/or 6- position are the Δ^3 -dihydropyrans with <u>cis</u> 2- and 6- substituents and the all-<u>cis</u>-2,4,6-trisubstituted tetrahydropyrans. Δ^3 -Dihydropyrans are shown to be formed <u>via</u> 2H-pyrans by a 1,4 reduction while tetrahydropyrans result from 4H-pyrans by reduction of both enol-ether double bonds.

Among the versatile reductions with acyloxyborohydrides, which were recently reviewed by Gribble,² the reduction of enamines has been thoroughly investigated.³ Apparently no such reduction has been applied successfully to the related enol-ethers or pyrans. In connection with our work on reduction of pyrylium salts,^{4,5} we have applied the title reduction to various substituted pyrylium salts and we present here the reaction pathways and products together with the synthetic utility of this novel reaction.

Pyrylium salts are easily accessible⁶ and very reactive towards nucleophiles in the 2and 6- (α -) or 4- (γ -) -positions; they are versatile synthons for various hetero- or carbocyclic compounds.⁷ We have shown earlier⁴ and it was later confirmed⁶ that the hydride ion generated by NaBH₄ in aqueous or alcoholic media adds to the α and γ positions of the pyrylium ring <u>1</u> to generate, on one hand, the unstable α -pyrans <u>2</u> and <u>2</u>⁴ which valence-tautomerize to *cis*-2-*trans*-4-pentadien-1-ones <u>4</u> and <u>4</u>⁴, and on the other hand, γ -pyrans <u>3</u> which are hydrolysed to 1,5-pentanediones <u>5</u> (see Scheme 1). Recently we have also shown that alkyl--substituted pyrylium salts can be hydrogenated catalytically affording in high yields the totally reduced products, namely the all-*cis*-alkyl-substituted tetrahydropyrans <u>7</u>.

The presently described reduction of pyrylium salts with NaBH(OAc)₃, i.e. with NaBH₄ in excess of acetic acid, is outlined in Scheme 1. The Table lists the various 2,4,6-trisubstituted pyrylium cations <u>la-li</u>, their anions, and the composition of the reduction mixture based either on GLC (<u>la-lf</u>) or on weighing the products separated by TLC (<u>le-li</u>). Under the reaction conditions,⁹ the conversion is quantitative for <u>la-lg</u>, but less than 50% for <u>lh</u> and <u>li</u> which, as will be shown further, behave differently.

The reduction of pyrylium cations <u>la-1g</u> with NaBH₄ in acetic acid medium occurs in two stages. The first stage is the same as for the reduction in neutral media,^{4,8} and is presented in the middle row of formulae in Scheme 1. In the second stage a further reduction occurs : the 2H-pyrans 2 and 2' give by addition of two hydrogen atoms the Δ^3 -dihydropyrans 6 and 6'.



TABLE. Pyrylium salts $\underline{1}$ and their reduction products (%) with NaBH, in AcOH *

1	R	Rʻ	R"	χΘ	α-addition			γ-addition		
1					6/6	<u>4+4</u> 1	3	<u>5</u>	<u>7</u>	version
a	Me	Me	Me	HOOC-CHSO	75	-	-	2	17	100
a'	Me	Me	Me	C104	78	-	-	5	12	100
Б	tBu	Me	tBu	C104	50	-	-	30	15	100
c	tBu	Me	Me	½SnCl ₆	30/43	-	-	7	15	100
ਰ	iPr	Ph	iPr	C10,	99 **	-	-	-	-	100
e	Me	Ph	Me	H00C-CH ₂ -SO ₃	98 **	-	-	-	-	100
f	Me	Me	Ph	C10,	46/0	3	-	26	25	100
a	Me	Ph	Ph	HOOC-CH2-SO3	<i>99</i> /0 **	-	-	-	-	100
ň	Ph	Me	Ph	C10,	-	28	47	19	-	35
ī	Ph	Ph	Ph	C104	-	77	13	-	-	45

* Major products (>75%) are italicized ; minor, unidentified products are not given ** Preparative yield of isolated product

On the other hand, four hydrogen atoms add to the 4H-pyrans $\underline{3}$ to afford tetrahydropyrans $\underline{7}$. The data from the Table can be summarized in the following points :

i. The effect of the anion (cf. $\underline{1a}$ and $\underline{1a}$) is negligible for the product distribution but the increased solubility of sulfoacetates is helpful.

ii. As seen from the italicized figures, α -addition is preferred owing to the reduced charge density in the α - compared to the γ -position of the pyrylium ring.⁶

iii.Dihydro- and tetrahydropyrans are the major products of pyrylium salts bearing at least one α -alkyl substituent (<u>1a-1g</u>). In <u>1a-1c</u> the ratio dihydro-/tetrahydropyran, i.e. (<u>6+6'</u>)/<u>7</u>, is consistent with the ratio of the α/γ attack of H⁻ to alkyl-substituted pyrylium salts.^{+,10} *iv*. Although somewhat less addition occurs in α -positions substituted with bulky groups, steric factors are unimportant for the α/γ (cf. <u>1b</u>) or α/α' (cf. <u>1c</u>) regioselectivity of the hydride nucleophile.Indeed, <u>1c</u> gives rise to comparable ammounts of 2-*t*-butyl-4,6-dimethyl--5,6-dihydro-2H-pyran (<u>6c</u>) and of the corresponding 3,6-dihydro-2H-pyran isomer (<u>6'c</u>). *v*. In contrast to *iv*, electronic factors are dominant and can be put to use in order to make this reaction regiospecific. Thus, a phenyl group in the α or γ position hinders the attack of the hydride nucleophile in the respective position, probably by charge delocalization. This effect is responsible on one hand for the quantitative yields in Δ^3 -dihydropyrans when a γ -phenyl group is present (from pyrylium salts <u>1d</u>, <u>1e</u> and <u>1g</u>), and on the other hand, when a 6-phenyl group is present, for the regiospecific formation of the 3,6-dihydro-2H-pyrans <u>6f</u> and <u>6g</u> and not of the isomeric 5,6-dihydro-2H-pyrans <u>6'f</u> and <u>6'g</u>. The latter regiospecificity is an interesting feature of Δ^3 -dihydropyran formation because if one admits the intermediacy of 2H-pyrans <u>2f</u> and <u>2g</u> (and not of <u>2'f</u> and <u>2'g</u> which would involve attack of the hydride nucleophile at the phenyl-substituted 6-position of the pyrylium ring), then the resulted 3,6-dihydro-2H-pyrans <u>6f</u> and <u>6g</u> must arise via a 1,4 reduction by triacetoxyborohydride.

We demonstrated that this is indeed the case by performing separately the two reduction stages for <u>le</u>. Thus, by reducing <u>le</u> rapidly at 0° with *aqueous* NaBH₄ following with extraction into diethyl ether and drying the organic layer at -10°, the first reduction stage was completed and the elusive 2H-pyran <u>2e</u> obtained. The ethereal layer was subsequently reduced in the second stage with NaBH₄ in *acetic acid* to give about 80% (by ¹H-NMR) of <u>6e</u>¹¹ (Scheme 2, X = Y = H). By replacing in the latter stage NaBH₄ with NaBD₄ we obtained 6-*d*-<u>6e</u> (X = D, Y = H).¹² By reducing <u>le</u> with NaBH₄ in *AcOD* we obtained 3-*d*-<u>6e</u> (X = H, Y = D).¹³ These facts are consistent with the mechanism depicted in Scheme 2, in which the nucleophile is transferred to the 2H-pyran from the opposite side of the 2-methyl group, accounting for the observed stereospecificity.



The preferred reduction pathway for 2H-pyrans with NaBH(OAc)₃ is thus a 1,4-addition and not a 1,2-addition at the enol-ether double bond. Reduction of enol-ether double bonds must be, however, the pathway for the 4H-pyrans 3 and is probably slower than the 1,4 reduction. It is noteworthy that the tetrahydropyrans $\underline{7}$ are all-*cis*, i.e. the same compounds which are obtained by hydrogenating catalytically pyrylium salts with alkyl substituents.⁵

Pyrylium salts which have phenyl groups in both α positions, e.g. <u>1h</u> and <u>1i</u> behave differently. The reduction with NaBH(OAc)₃ leads for these salts to products resulting *only* by addition of two hydrogen atoms, as in the case of aqueous NaBH₄ reduction.¹⁴ Thus the second reduction stage is inoperant, i.e. the 2,6-diphenyl substituted 2H- and 4H-pyrans resist further reduction with NaBH(OAc)₃. The final products are in this case the dienones <u>4h</u> and <u>4i</u>, along with the 4H-pyrans <u>3h</u> and <u>3i</u>.

When the stabilizing effect of two α -phenyl groups is absent (<u>3a-3g</u>), any 4H-pyran which is not reduced in the second stage and remains in the reaction mixture is hydrolysed during the final aqueous workup to the corresponding 1,5-diketones <u>5</u>, as shown by control GLC experiments. 1,5-Diketones are by-products in all cases in which γ -addition is not inhibited (i.e. when a 4-methyl group is present).

In conclusion, the present reduction of pyrylium salts with NaBH(OAc)₃ which gives mostly Δ^3 -dihydropyrans by the above described mechanism with a previsible regio- and stereochemistry may prove of interest in the preparation of such compounds, free of any other unsaturated isomer, taking into account that these are difficultly accessible otherwise.¹⁵ The formation of Δ^3 -dihydropyrans from pyrylium salts, ammounting to a global addition of 4[H], is inter-

mediate between the reduction in neutral medium with $NaBH_4$ (addition of 2[H]) and the catalytical hydrogenation (addition of $3H_2$). The pyrylium route provides by the now available reductions a promising stereoselective entry to non-aromatic six-membered oxygen-containing heterocycles.

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References and Notes

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- 12. ¹H-NMR for 6-d-6e: no signal at 4.36 ppm ; this spectrum is similar to the decoupled spectrum of 6e by irradiating at 4.36 ppm, indicating 6-monodeuteration.
- 13. ¹H-NMR for 3-d-<u>6e</u> : quintet at 3.76 ppm and reduced m at 2.30 ppm indicating 3-monodeuteration ; the H6 multiplet is less broad than in <u>6e</u> owing to the dissappearance of the coupling between the pseudoaxial H3 and H6 protons.
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