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Received October 28, 1974

Levulinic Esters. An Alcohol Protecting Group Applicable to Some Nucleosides[1]

Sir:

Protection and mild deprotection of alcohols is of considerable importance in natural products chemistry, especially in carbohydrates, nucleosides, and steroids.[2]

We considered the desirability of a protecting group X so that deprotection occurs after a mild operation (y) that transforms X into a new function Z (see eq 1). Ideally ROZ

$$\mathrm{ROH} \longrightarrow \mathrm{ROX} \xrightarrow{y} \mathrm{ROZ} \longrightarrow \mathrm{ROH} \qquad (1)$$

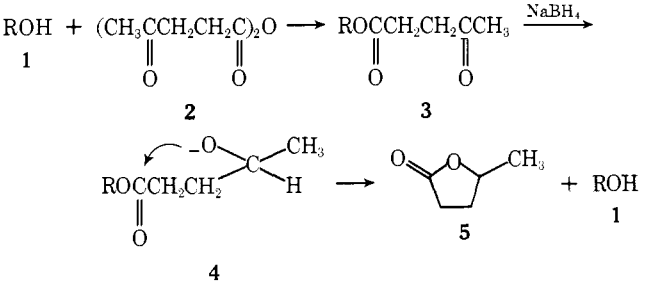
should spontaneously regenerate the alcohol. Such examples include the formation of a tiglic ester[3] which is deprotected by OsO_4-HIO_4 oxidation or benzoylpropionic acid esterification[4] followed by hydrazinolysis.

We wish to report the protection of alcohols by formation of their levulinates, **3,** and the successful mild deprotection of the latter with $NaBH_4$. The method is based on two principles: (1) selective reduction of ketones over esters by borohydride so that ester and other functions can be present in the molecule; (2) facile intramolecular lactone formation from γ-hydroxy esters (see **4**) with concomitant release of ROH. The water soluble lactone **5** is easily separated from the product and was in fact isolated and identified in one of the experiments. In principle any nucleophile capable of attacking the carbonyl group of ketones (cf. **3**) may be suitable. However, only partial success was achieved with the mild nucleophiles CN^- or HSO_3^-, while H^- ($NaBH_4$) in dioxane–water at 25° (30 min) or in alcohol at 65° (1 min) proved to be the most convenient. Another advantage of using $NaBH_4$ is that, if necessary, the pH range of the reaction can be varied between 5 and 8.5 by simultaneous addition of acid,[5] since carbonyl reduction by this reagent occurs readily in this pH range.

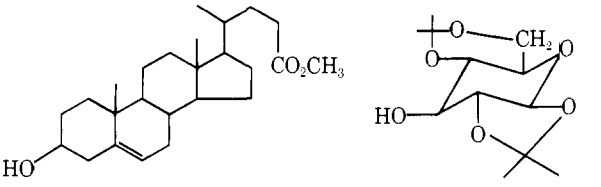
Table I. Levulinate Protection and Deprotection of Alcohols

Entry	Alcohol 1	Levulinates[b] % yield[a]	Mp, °C	Yield (%)[a] of pure recovered 1
1	*p*-Nitrobenzyl	80	58	93
2	Cholesterol	74	66.5–68	97
3	Epicholestanol	76	104–105	78
4	**6**	67	96–97	65
5	**7**	67	79	94
6	2′,3′-Di-O-benzoyl uridine (**8a**)	86	156	82
7	2′,3′-Isopropylidene-uridine (**8b**)	90	45	94
8	5′-O-Tritylthymidine (9)	81	143–145	90

[a] Yield usually refers to recrystallized material. [b] All compounds showed consistent elemental analyses, ir, and NMR spectra.



Successful protection and deprotection of several alcohols shown in Table I was achieved in the presence of nitro, olefin, ester, and acetal (entries 1, 2, 4, and 5) functions. Furthermore, the examples include an axial alcohol (entry 3) as



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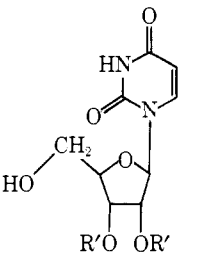
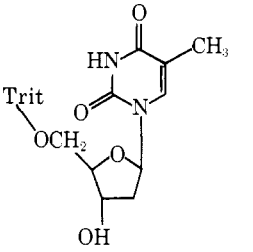


8a, R′ = Ph—C(=O)—

b, R′R′ = $C(CH_3)_2$



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well as several nucleosides. Of particular interest are the successful protection and deprotection of uridines, **8**, in the presence of the 2′,3′-di-*O*-benzoyl function, of a 5′-*O*-trityl protected thymidine[6] **9**, and the fact that the levulinates are stable in 80% acetic acid over a 48-hr period and in trifluoroacetic acid for 20 hr. Furthermore in at least six cases, the borohydride reduction and the consecutive lactonization appeared to be quantitative as determined by TLC. The yields reported are those of recrystallized material.

The levulinates had to be prepared via levulinic anhydride **2** since levulinyl chloride[7] leads to pseudo esters that are very labile to basic hydrolysis.[8]

Levulinic anhydride **2** was obtained in quantitative yield by reaction of levulinic acid (20 mmol) with dicyclohexylcarbodide (10 mmol) in 65 ml of ether for 5 hr followed by filtration and evaporation of the solvent. A solution of 10 mmol of **2**, and 5 mmol of **9** in 10 ml of anhydrous pyridine was kept for 24 hr, ice water was added, and the levulinate **3** (100%) crystallized from benzene–hexane mp 143–145° (81%). A solution of 0.25 mmol of the levulinate in 2 ml of dioxane was treated with 37 mg of $NaBH_4$ in 0.5 ml of water for 20 min, the pH was brought to 5 (HOAc), and the mixture was poured onto ice. 5′-*O*-Tritylthymidine (**9**) was filtered (90%), mp 128°.

Acknowledgment. Support of this research by grants from the National Cancer Institute (CA 04474 to A.H.) and from the National Institutes of Health (AM 05098 to A.P.) is gratefully acknowledged.

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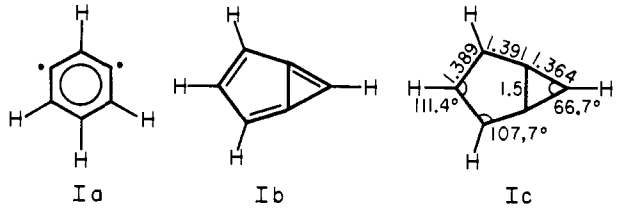
Received September 30, 1974

Generation of Bicyclo[3.1.0]hexatriene. A Reactive Intermediate

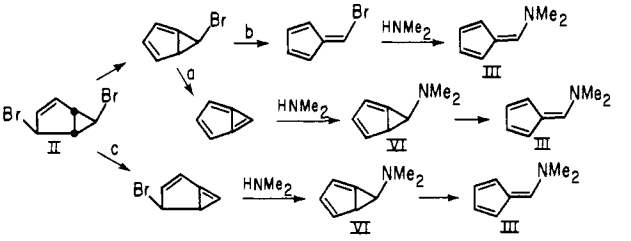
Sir:

Of the three dehydrobenzenes possible, 1,3-dehydrobenzene or *m*-benzyne (I) has received the least consideration.



Ia Ib Ic

Scheme I



We wish to describe the synthesis of I and the results of theoretical calculations pertaining to I. To date, the only report of I is that of Berry detailing the results of the flash pyrolysis of *m*-benzenediazonium carboxylate.[1]

Two distinct geometrical representations are possible for *m*-benzyne: a hexagonal conformation (Ia) resembling that of benzene or a bicyclo[3.1.0]hexa-1,3,5-triene (Ib). Until very recently all theoretical studies of *m*-benzyne had considered only the hexagonal conformation Ia and had consequently focused upon the multiplicity of the ground state.[2,3] However, MINDO/3 calculations led Dewar to predict, after geometry optimization, the ground state to be represented by structure Ib, in which the C_1–C_5 separation was reduced from 2.41 Å in structure II to 1.97 Å.[4] Furthermore, his studies represent the first suggestion that *m*-benzyne would be a singlet of stability comparable to that of *o*-benzyne.

In our approach to *m*-benzyne, we sought suitable precursors containing the σ framework. Such a precursor was *exo-exo*-2,6-dibromobicyclo[3.1.0]hex-3-ene (II), readily available from benzvalene.[5] II was a particularly desirable precursor since the exo stereochemistry of the halogens favored the initial 1,4-elimination of HBr to form a cyclopentadiene. Subsequent ionization should be particularly favorable since ring strain would be relieved. Eventual loss of halide from C_6 would generate I.

The dropwise addition of II to a tetrahydrofuran solution containing 3 equiv of potassium *tert*-butoxide (0.33 *M* in potassium *tert*-butoxide and 0.56 *M* in dimethylamine)[6] at −75° under argon after 5 min generated 6-dimethylaminofulvene (III)[7] in 90% yield. In addition, *exo-exo*-2-dimethylamino-6-bromobicyclo[3.1.0]hex-3-ene[9] and 6-*tert*-butoxyfulvene[10] (IV) were formed in 7 and 2% yields, respectively.

Any of three pathways can account for the formation of the 6-dimethylaminofulvene (III) (Scheme I). Only one, path a, requires the intermediacy of *m*-benzyne. Nucleophilic addition of dimethylamine at the electron deficient carbon C_6 of I would form 6-dimethylaminobicyclo[3.1.0]hexa-1,3-diene (VI) after protonation. A [1.5]-sigmatropic shift of C_6 from C_5 to C_1 converts VI to III. VI is a logical precursor of III since precedence exists for facile 1,5-alkyl migration in ring systems containing a strained cyclopentadienyl ring.[12]

In one alternative pathway, path b, a 6-halogenated fulvene would be an obligatory intermediate. If *m*-benzyne were sufficiently destabilized due to strain, the second HBr elimination need not occur from II. Instead, a 1,5-alkyl migration of C_6 in the intermediate 6-bromobicyclo[3.1.0]hexa-1,3-diene results in the formation of 6-bromofulvene which would subsequently react to form III.[14] However, the intermediacy of a halogenated fulvene was discredited by treating II as above with potassium *tert*-butoxide but in the absence of dimethylamine. In less than 5 min II was completely converted to 6-*tert*-butoxyfulvene (IV) and several minor products, two of which have been identified as bromobenzene and 6-bromofulvene. 6-Bromofulvene cannot be the precursor of the 6-*tert*-butoxyfulvene since, under