min the mixture was kept at room temperature for further 1 min and then was quenched in ice (1.5 kg) containing hydrochloric acid (150 mL, 37%). The suspension was warmed to 50 °C for 5 min, cooled, and extracted with ethyl acetate. The crude product (250 mg) was recrystallized from acetic acid as dark red needles: mp >320 °C dec; IR (KBr) 3400, 1675, 1620, 1570 cm^{-1}; UV λ_{max} 276, 312, 350, 466, 498, 538 (log ϵ 4.52, 4.12, 3.72, 3.90, 3.96, 3.76); ^{1}H NMR (DMSO-d_6) δ 13.7 (s, 1 H, OH, exchangeable with D_2O), 11.4 and 13.0 (2 H, 2 × br s, 2 OH, exchangeable with D_2O), 7.7 (1 H, s, H-4), 6.7 (1 H, s, H-7), 2.70 (3 H, s, CH_3); mass spectrum, *m/e* 330 (M^+). All these properties were in agreement with the literature.[9] Mixture melting point with a sample obtained according to Cameron et al.[9] was >320 °C.

9,10-Dioxo-3,5,6,8-tetramethoxyanthracene-2-carboxylic Acid Methyl Ester (4c). The trimethoxyanthraquinone **4b** (500 mg) dissolved in diethyl ether–methanol (250 mL) was treated with excess diazomethane. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to afford the tetramethoxyanthraquinone **4c** (480 mg): mp 196–198 °C (from methanol); IR 1720, 1660 cm^{-1}; UV λ_{max} 415, 280, 269 (log ϵ 4.47, 4.45, 3.79); ^{1}H NMR δ 7.55 (1 H, s, 4-H), 6.81 (1 H, s, 7-H), 4.01 (6 H, 2 × s, overlapping, OMe at C-5, and C-8), 3.96 (9 H, 3 × s, overlapping, OMe at C-3, -6, and COOMe), 2.65 (3 H, s, CH_3); ^{13}C NMR δ 18.6 (q, Me at C-1), 56.3 (q, COOMe), 56.3, 56.3, 57.3 (3 × q, OMe at C-3, -6 and -8), 61.6 (q, OMe at C-5), 103.7 (d, C-7), 106.3 (d, C-4), 183.1 and 183.6 (2 × s, quinone carbonyls), 127.7, 128.0, 137.2 (4 × s, C-4a, -8a, -9a, and -10a), 130.8, 143.5, 157.5, 157.5, 158.6, 158.6 (6 × s, C-1, -2, -3, -5, -6, and -8), 167.7 (s, COO); mass spectrum, *m/e* 400 (M^+).

Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.0; H, 5.0. Found: C, 63.2; H, 4.9. All these physicochemical properties and mmp show that the compound was identical with that obtained by the reported route.[9,10]

Acknowledgment. This work was supported by the Ministero della Pubblica Istruzione and by the Davide Campari S.p.A. Milano.

Registry No. 1a, 1260-17-9; **1b**, 18499-92-8; **2a**, 110551-54-7; **2b**, 110551-55-8; **4a**, 110551-56-9; **4b**, 110551-57-0; **4c**, 69119-28-4.

Lactone Formation in the Oxidation of Diols with *N*-Iodosuccinimide and Silver Acetate

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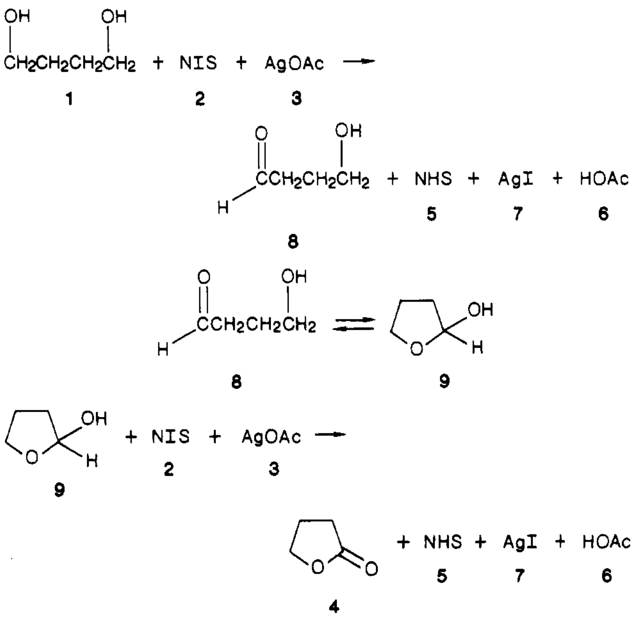
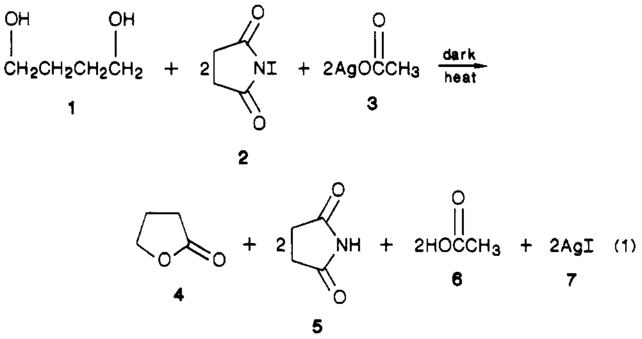
Recently,[1] we found that primary and secondary alcohols were oxidized to aldehydes and ketones when treated in the dark with *N*-iodosuccinimide (NIS), silver acetate, and heat. Tertiary alcohols were unaffected when subjected to these same reaction conditions. In this new study we have oxidized four symmetrical diprimary diols (1,4-butanediol, 1,5-pentanediol, 1,6-hexanediol, and 1,2-benzenedimethanol) and one unsymmetrical primary, tertiary diol (α,α-dimethyl-1,2-benzenedimethanol) with NIS in the presence of silver acetate with heat in the absence of light. Lactones were found to be the products of the diol oxidations. The proposed last chemical step in the formation of the lactones from the primary diols is the oxidation of cyclic hemiacetals with NIS and silver acetate, a new reaction for *N*-iodosuccinimide and hemiacetals. Under light-catalyzed radical conditions the hypoiodite of the cyclic hemiacetal **9** undergoes carbon–carbon bond cleavage to produce γ-iodopropyl formate.[2] The pathway of the decomposition of the cyclic hemiacetal hypoiodites depends on whether it is irradiated or heated with silver acetate in the absence of light. Lactone preparation[3] from diols has been reported by previous authors using a variety of oxidizing agents although none has formed hypoiodites of hemiacetals in their procedures.

Scheme I



The formation of the lactone products can be illustrated by a discussion of the oxidation of 1,4-butanediol (**1**) with NIS (**2**) and silver acetate (**3**). When the diol **1** is mixed with the solvent benzene, **2**, and **3** and heated, the products found on the gas chromatograph are γ-butyrolactone (**4**) (80–85%) and acetic acid (**6**) (85–89%) as shown in eq 1.



The stoichiometry in eq 1 also is supported by good yields of succinimide (**5**) and silver iodide (**7**). The formation of the γ-butyrolactone in good yield indicates a probable nonradical pathway for the NIS/silver acetate oxidation of diols to lactones.

We believe that the diol-to-lactone conversion occurs in two steps as shown in Scheme I. Here 1,4-butanediol (**1**) is first oxidized to the hydroxy aldehyde **8** which is in

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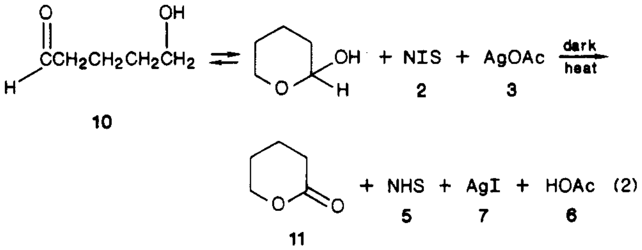
Table I

diol	products	(time, h; yield, %)
1,4-butanediol	γ-butyrolactone	(5–7; 80–85)
1,5-pentanediol	δ-valerolactone	(5–7; 72–80)
1,6-hexanediol	ε-caprolactone	(5–6; 18–23)
1,2-benzenedimethanol	phthalide	(3–4; 75–90)
5-hydroxypentanal	δ-valerolactone	(2–3; 82–90)
α,α-dimethyl-1,2-benzenedimethanol	α,α-dimethylphthalide	(16–18; 80–90)

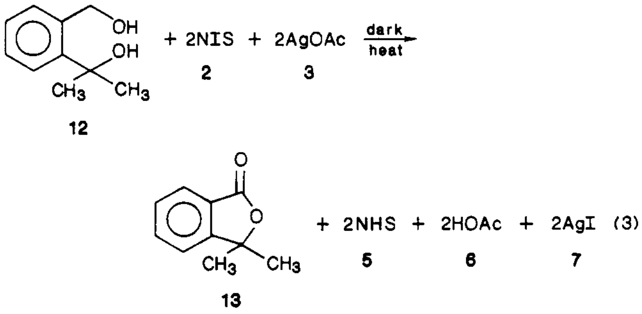
equilibrium with the cyclic hemiacetal 9. Further oxidation of 9 with NIS and silver acetate would give the γ-butyrolactone (4) product. The lactone products indicate a silver ion catalyzed[4] decomposition pathway for the alkyl hypoiodites[5] that are thought to be the initial products when NIS and alcohols react.

To support the diol-to-hydroxy aldehyde-to-lactone concept, we oxidized 5-hydroxypentanal (10) with NIS and silver acetate as shown in eq 2. The expected δ-valerolactone (11) was produced in 82–90% yields.



Good yields, determined from VPC and HPLC analysis, see Table I, were obtained for two 1,4-diols (1,4-butanediol and 1,2-benzenedimethanol) and for 1,5-pentanediol. We obtained only 18–23% yields of lactone when 1,6-hexanediol was oxidized with NIS and silver acetate.

Oxidation of the unsymmetrical diol is illustrated in eq 3 where α,α-dimethyl-1,2-benzenedimethanol (12) was converted to α,α-dimethylphthalide (13) (1 h, 30%; 3 h, 53%; 18 h, 90%) with the NIS/AgOAc reagents. The



oxidation of the unsymmetrical diol takes advantage of the lack of reaction of tertiary alcohols toward the NIS/AgOAc oxidizing agent. We believe the primary alcohol is oxidized to an aldehyde which forms a cyclic hemiacetal with the tertiary alcohol. The cyclic hemiacetal is then oxidized in good yield to the lactone 13. The NIS and silver acetate reagents offer a good alternate method of producing lactones from symmetrical diprimary diols and from unsymmetrical primary, tertiary diols.

Experimental Section

Analyses were performed on Varian Model 3400, Varian Model 3700, and Hewlett-Packard Model 5700A VPC instruments and a Waters HPLC system comprised of two Model 501 pumps with automatic gradient control and a Model 440 UV detector. VPC analyses were done on 6 ft × 0.25 in. copper columns of 10% Carbowax 20M and a 7% SE-30/3% Carbowax 20M mixture on Chromsorb P and Chromosorb W. The HPLC column used 0.46 × 15 cm Chromosil, 5 μm C18 packed, with UV detection at 254 nm.

The benzene and acetonitrile solvents were spectroscopically pure and were used without further purification. Chemicals needed in the reactions were used as purchased. Liquid chemicals were spectroscopic grade and used without further purification. The NIS was determined to have 98–99.5% active iodine and was used as purchased.

Oxidation of 1,4-Butanediol with NIS and Silver Acetate in the Dark with Heat. A mixture of 0.514 g (2.285 mmol) of NIS, 0.103 g (1.143 mmol) of 1,4-butanediol, and 0.366 g (2.193 mmol) of silver acetate was placed in a 10-mL round-bottomed flask fitted with a condenser and a $CaCl_2$ drying tube. Five milliliters of benzene was added to the flask. The flask was protected from light. The mixture was stirred and heated at reflux. Reaction times and lactone percentage yields were as follows: 1 h (11%), 2.3 h (40%), 3 h (51%), 5 h (71%), 6.5 h (76%), 7 h (82%), 7.5 h (89%). Silver iodide was recovered in 90% yield and succinimide was found in 60% yield.

Oxidation of 1,5-Pentanediol with NIS and Silver Acetate in the Dark with Heat. A mixture of 0.220 g (1.015 mmol) of NIS, 0.170 g (1.018 mmol) of silver acetate, and 0.0530 g (0.51 mmol) of 1,5-pentanediol was placed in a 10-mL round-bottomed flask fitted with a condenser and a $CaCl_2$ drying tube. Five milliliters of benzene was added to the flask. The mixture was stirred and heated at reflux for 7 h in the dark (aluminum foil covered flask). Reaction times and percentage yields (VPC analyses) of δ-valerolactone and acetic acid, respectively, were as follows: 1 h (53, 13), 2 h, (69, 38), 4 h (68, 66), 6 h (80, 83), and 7 h (77, 85). Succinimide was recovered in 79% yield (crude, mp 90–111 °C, recrystallized mp 110–117 °C). Silver iodide was recovered in 82% yield.

Preparation of α,α-Dimethyl-1,2-benzenedimethanols.[6] This unsymmetrical diol was synthesized by the addition of excess methylmagnesium bromide to the lactone, phthalide.

Oxidation of α,α-Dimethyl-1,2-benzenedimethanol with NIS and Silver Acetate. HPLC Lactone Preparative Run. A mixture of 5.12 g (31.2 mmol) of α,α-dimethyl-1,2-benzenedimethanol, 10.5 g (63.0 mmol) of dry silver acetate, 14.2 g (63.5 mmol) of NIS, and 25 mL of dry benzene was added to a 100-mL flask. A condenser with a $CaCl_2$ drying tube was connected to the flask. The mixture was stirred and heated at reflux in the dark for 14 h. Vacuum filtration removed the sliver iodide and succinimide products. Evaporation of the filtrate gave 4.80 g of oily crude lactone product. The crude product was dissolved in dichloromethane and washed with 5% $NaHSO_3$ and with water. The solvent was removed and the crude lactone was redissolved in acetonitrile. Purification of the residual lactone by preparative HPLC produced 3.80 g (75% yield) of lactone crystals, mp 63–65 °C. Recrystallization of these crystals in cyclohexane gave pure lactone, mp 67–68 °C (lit.[7] mp 68–69 °C). IR analysis gave a carbonyl absorption band at 1770 cm^{-1} and a dimethyl doublet at 1387 and 1372 cm^{-1}. NMR analysis gave a singlet (δ 1.7) and a multiplet (δ 7.3–8.0) with the expected area ratios of 6:4.

Oxidation of α,α-Dimethyl-1,2-benzenedimethanol with NIS and Silver Acetate. HPLC Quantitative Analysis. A solution (5 mL) of 0.243 g (1.33 mmol) of α,α-dimethyl-1,2-

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benzenedimethanol and 0.143 g (1.28 mmol) of chlorobenzene in acetonitrile was added to 0.446 g (2.55 mmol) of dry silver acetate and 0.570 g (2.52 mmol) of NIS contained in a 10-mL flask. A condenser with a drying tube was connected to the flask. The mixture was stirred and heated at reflux in the dark (aluminum foil covered the flask) for 18 h. A 1-mL sample was removed and was filtered through a 5-μm filter with the use of a centrifuge. The sample was analyzed on an HPLC with chlorobenzene as an internal standard. The yields of lactone was 90% in 18 h. Silver iodide was recovered in 55% yield.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Registry No. **1**, 110-63-4; **2**, 516-12-1; **3**, 563-63-3; **4**, 96-48-0; **9** (hypoiodite deriv), 110590-71-1; **10**, 4221-03-8; **11**, 542-28-9; **12**, 55549-01-4; **13**, 1689-09-4; $HO(CH_2)_5OH$, 111-29-5; $HO(CH_2)_6OH$, 629-11-8; $2\text{-}HOCH_2C_6H_4CH_2OH$, 612-14-6; $I(CH_2)_3O_2CH$, 110590-72-2; ε-caprolactone, 502-44-3; phthalide, 87-41-2.

The Difference between Hydrogen and the Methyl Group as Electrophilic Centers in β-Elimination Reactions

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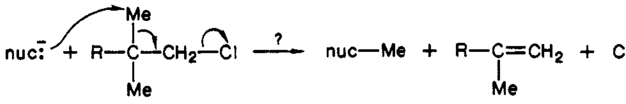
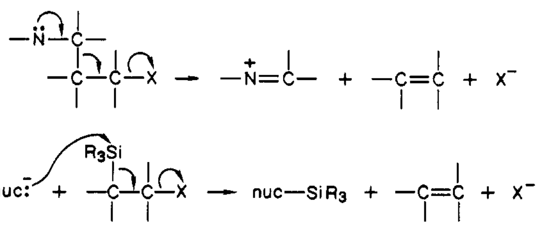
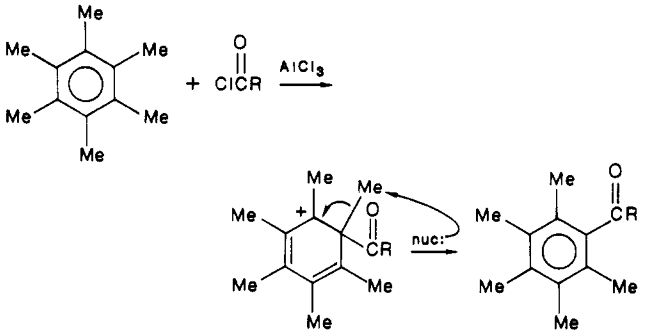
A methyl group often reacts like a hydrogen in organic reactions. When bonded to a metal and carrying a significant negative charge, each serves as a strong nucleophile (e.g., MeLi and LiH). When bonded to a halogen and carrying a significant positive charge, each serves as an electrophilic center (e.g., MeCl and HCl). When carrying no significant charge, each is usually unreactive as a nucleophile or electrophile. Important exceptions to this generalization occur, however, such as nucleophilic abstraction of a hydrogen from a carbon β to a leaving group in an elimination reaction. To our knowledge, however, no one has explored the possibility of a β-elimination, where a nucleophile abstracts a methyl group instead of a hydrogen.



1a, R = Ph
b, R = Me
c, R = 4-$NO_2C_6H_4$

Three comparable reactions nurtured our belief in the possibility of this untested elimination. The intramolecular electron flow of fragmentation reactions[1] runs parallel to the proposed elimination reaction, although here the nucleophilic nitrogen is already bonded to the carbon to be abstracted. Also the β eliminations where a nucleophile abstracts a trialkylsilyl group[2] proceed by the desired kind of electron flow. Finally, the second step of an anomalous Friedel–Crafts acylation[3] probably features a methyl abstraction to yield a carbon–carbon double bond.





We decided to test the novel elimination on three electrophiles expected to be favorably disposed toward the reaction. The first was 1-chloro-2-methyl-2-phenylpropane (neophyl chloride, **1a**), a candidate due to its lack of competing β hydrogens and the reluctance of its neophyl structure to undergo either S_N1 or S_N2 substitution. First, **1a** was mixed with a nucleophilic salt, either LiCl or NaCN, in DMF, a rate-enhancing, polar, aprotic solvent. After 22 h at 100 °C and a further 22 h at 125 °C, the NMR of the reaction mixtures showed no reaction. Finally, after a further 4 days at reflux (~153 °C), the NMR showed signs of reaction. Chloride nucleophile converted **1a** to 2-methyl-1-phenyl-1-propene. This unexceptional product doubtless resulted from a phenyl shift on the neophyl carbocation, followed by ordinary E1 elimination. On the other hand, cyanide, an extremely strong nucleophile in DMF,[4] left mostly starting material as well as a compound with no vinyl protons, probably the substitution product, 3-methyl-3-phenylbutanenitrile. With neither salt was any desired product, 2-phenyl-1-propene, observed.

Next, **1a** was combined with a nucleophilic amine, either morpholine or Bu_3N, as the solvent to increase the probability of collision between nucleophile and electrophile. The reaction mixtures were heated at 123–129 °C for 2 days. Although deep red colors developed, the NMR spectra showed only starting materials.

To avoid the unwanted phenyl shift of **1a**, an electrophile with only methyl groups in the β position, 1-chloro-2,2-dimethylpropane (neopentyl chloride, **1b**), was subjected to nucleophiles. After heating **1b** with LiCl or NaCN in DMF at 200 °C for 2 days in a sealed bomb, NMR showed only starting materials. Reaction was observed when **1b** was heated in morpholine at 200 °C for 3 days in the bomb. NMR indicated a solid product to be morpholine hydrochloride, while the liquid component appeared to contain the substitution product, *N*-neopentylmorpholine. But no sign of *N*-methylmorpholine, the product of a methyl abstraction, was observed.

Finally, the novel elimination was tried on the third electrophile, 1-chloro-2-methyl-2-(4-nitrophenyl)propane (**1c**). Its electron-withdrawing nitro group provides **1c** with two advantages over its analogue, **1a**: diminished tendency to undergo undesirable phenyl shift and somewhat diminished electron density (i.e. increased electrophilicity) at the methyl group to be abstracted. Yet after refluxing for 1 day, a mixture of **1c** and NaCN in DMF indicated no reaction by NMR. Refluxing a solution of **1c** in morpholine for 3 days allowed perhaps a little substitution of

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