The Tiglate Ester as an Alcohol Blocking Group in Organic Synthesis[1]

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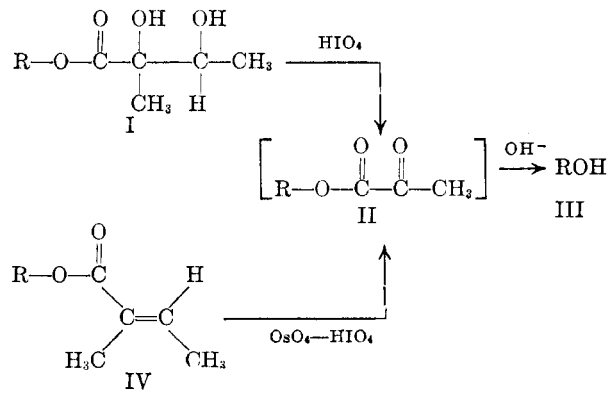
Received April 5, 1962

The effective use of the tiglate ester as an easily formed and readily cleaved alcohol blocking group is described.

In syntheses which involve nonphenolic polyhydroxy compounds, the need often arises for blocking one or more hydroxyl groups while another is esterified. There are relatively few general methods available for selective hydroxyl blocking with subsequent regeneration of the hydroxyl function under conditions which would not hydrolyze other ester groups in the molecule. Sequences involving formation of readily solvolyzed acyl esters,[2,3] acid-labile 2-tetrahydropyranyl,[4] methoxymethyl,[5] or triphenylmethyl[6] ethers, or readily hydrogenolyzed benzyl ethers[7] have been used effectively on occasion. However, each procedure is somewhat limited in scope. The use of partial solvolysis is limited to those polyol derivatives in which appreciable selectivity toward solvolysis exists. The use of 2-tetrahydropyranyl and of trityl ethers is limited by the fact that only primary and relatively unhindered secondary alcohols appear to form the respective ether derivatives. Methoxymethyl and benzyl ethers are prepared under strongly alkaline conditions, and their use is consequently precluded for base-sensitive compounds. We report herein the effective use of the tiglate ester as an easily formed and readily cleaved alcohol blocking group.

The key selective reaction upon which the effectiveness of the tiglate blocking sequence is based is the exceedingly facile alkaline hydrolytic cleavage of pyruvate esters.[8] The latter phenomenon was utilized to good advantage in the highly selective cleavage of the α,β-dihydroxy-α-methylbutyrate residue from the alkaloid tetraester protoveratrine B[9] and related compounds.[10,11] Periodate oxidation of the glycol ester yielded a pyruvate ester; mild alkaline treatment led to highly selective hydrolysis of the pyruvate (I–III).



The present investigation was undertaken to evaluate the use of an α,β-unsaturated-α-methylbutyrate group as an easily introduced ester which could be cleaved to pyruvate by osmium tetroxide–periodate oxidation.[12] The first studies involved the preparation of representative tiglate esters for studies of the cleavage reaction. The tiglate esters of *p*-nitrobenzyl alcohol and of cholestane-3-β-ol were prepared in the usual manner. The esters were treated with osmium tetroxide-periodic acid in aqueous dioxane for three hours, and then with dilute base at room temperature, whereupon 80–90% yields of the respective alcohols were obtained. To evaluate whether the reaction would be applicable to a tiglate ester of a periodate-sensitive alcohol, *p*-bromobenzoylcarbinol tiglate was next subjected to osmium tetroxide–periodic acid cleavage. Excess periodic acid was destroyed prior to alkaline hydrolysis of the pyruvate ester by adding decinormal alkaline sodium arsenite solution. Cleavage to *p*-bromobenzoylcarbinol tiglate was achieved in 79% yield.

The use of the tiglate group as an alcohol blocking group is exemplified in the sequence V → VII for the synthesis of strophanthidol 3-acetate. Direct partial acetylation of strophanthidol (V) was shown to attack preferentially the primary alcohol group at C-19 and yield strophanthidol 19-acetate. Partial acylation with tigloyl chloride

(1) This investigation was supported by research grants from the Smith Kline and French Foundation and from the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

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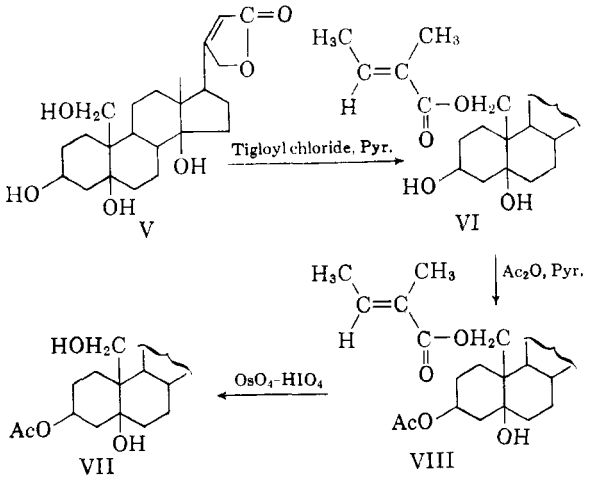
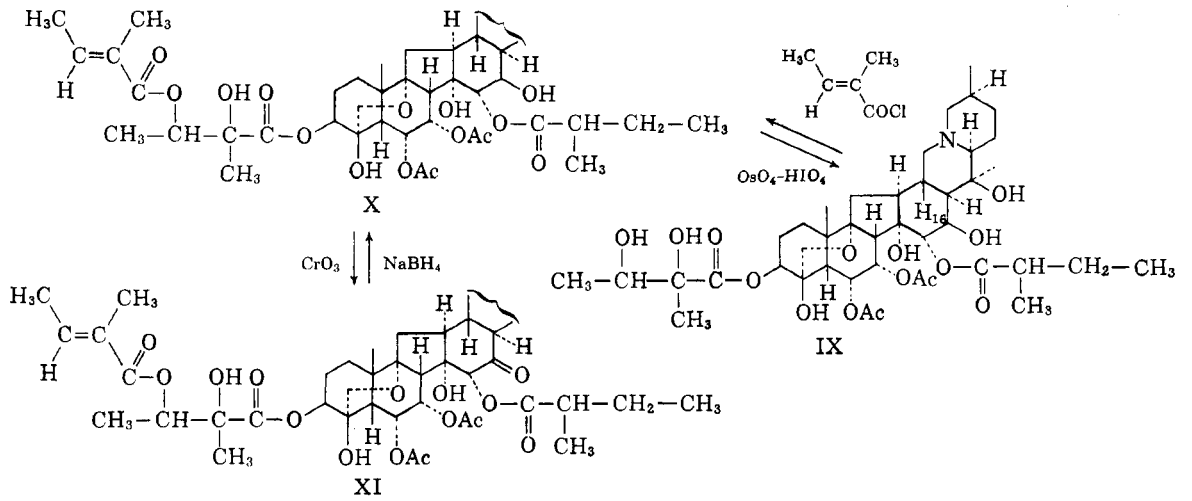


yielded strophanthidol 19-tiglate (VI). Acetylation of VI afforded strophanthidol 3-acetate 19-tiglate (VIII). Osmium tetroxide–periodic acid treatment of VIII removed the tiglate blocking group to yield strophanthidol-3-acetate (VII), identical with the product prepared by aluminum amalgam reduction of strophanthidin 3-acetate.[13] It is noteworthy that the unsaturated lactone in VIII was not appreciably attacked by the excess osmium tetroxide–periodic acid reagent. Clearly, the tiglate blocking sequence is applicable to some olefinic compounds which contain osmium tetroxide -insensitive double bonds.



In a continuation of our studies on the relationship between structure and hypotensive activity among analogs of the protoveratrines,[14–16] the synthesis of 16-epiprotoveratrine B was attempted. The planned approach involved blocking the secondary hydroxyl group in the 3′-position of the dihydroxymethylbutyrate residue at C-3 in protoveratrine B (IX), oxidizing with chromic acid to the 16-ketone (XI), reducing with sodium borohydride to a mixture of the 16-epimeric alcohols.[17] and, finally, removing the 3′-blocking group from the appropriate 16-alcohol to yield 16-epiprotoveratrine B. In fact, oxidation of protoveratrine B 3′-tiglate (X)[16] did yield the desired ketone (XI). However, sodium borohydride reduction of XI yielded X as the only isolable product, and the sequence therefore failed as an approach to 16-epiprotoveratrine B, because of the unsatisfactory course of the borohydride reduction. Nevertheless, to illustrate the potential value of the tiglate ester-blocking sequence, osmium tetroxide–periodic acid cleavage of protoveratrine B 3′-tiglate (X) afforded protoveratrine B (IX) in 60% yield.

Experimental[18]

p-**Nitrobenzyl Tiglate.**—Tiglic acid (0.500 g., Aldrich Chemical Co.) was suspended in water, and sufficient sodium hydroxide solution added until the solution was neutral. Two drops of concd. hydrochloric acid were added and the solution was added to *p*-nitrobenzyl bromide (1.00 g.) in ethanol (5 ml.) and heated under reflux for 2 hr. On cooling, an oil separated which was extracted with ether; evaporation to dryness left a solid residue. The solid was crystallized from ethanol to yield *p*-nitrobenzyl tiglate (0.426 g.), m.p. 62–64°. Recrystallization from ethanol gave an analytical sample, m.p. 63–64.°

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57. Found C, 61.54, H. 5.67.

Osmium Tetroxide–Periodic Acid Cleavage of *p*-Nitrobenzyl Tiglate.—To a stirred solution of *p*-nitrobenzyl

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(18) Melting points, determined on a Fisher-Johns hot stage, are corrected. Values of $[\alpha]_D$ have been approximated to the nearest degree. Uitraviolet absorption spectra were determined on a Model 11 MS Cary recording spectrophotometer and 95% ethanol was used as solvent. Infrared spectra were determined on solutions in chloroform on a Beckman Model IR5 spectrophotometer with NaCl prism and plates, using 0.1-mm. sodium chloride cells. Microanalyses were carried out by Dr. S. M. Nagy and his associates at the Massachusetts Institute of Technology,

tiglate (0.400 g.) in purified dioxane (15 ml., distilled from potassium hydroxide, passed through alumina, then redistilled) and water (5 ml.) was added osmium tetroxide (30 mg.). After a few minutes, a black color developed. Periodic acid (0.910 g.) was added and the solution was stirred for 3 hr. at room temperature. The reaction mixture was poured into 0.1 *N* sodium arsenite solution (270 ml., pH 8.5) containing one crystal of potassium iodide. The solution was stirred for 15 min. and extracted with ether. Evaporation to dryness left a solid which was recrystallized from carbon tetrachloride to yield *p*-nitrobenzyl alcohol (0.216 g., 82%), m.p. 92–93° (reported m.p. 93°[19]).

Cholestane-3β-ol Tiglate.—A solution of cholestane-3β-ol (2.000 g.) in benzene (10 ml.) and pyridine (10 ml.) was treated with tigloyl chloride[20] (0.50 ml.). The solution was heated under reflux for 3 hr. Evaporation to dryness under reduced pressure left a solid residue which was suspended in 5% sodium bicarbonate solution and extracted with ether. Evaporation of the ether and crystallization of the solid residue from ethanol gave cholestane-3β-ol tiglate (1.860 g.), m.p. 105–108°. Recrystallization from ethanol gave an analytical sample, m.p. 107–108°, $[\alpha]^{29}D$ + 17° (*c* 1.07, chloroform).

Anal. Calcd. for $C_{32}H_{54}O_2$: C, 81.04; H, 11.56. Found: C, 81.01; H, 11.51.

Osmium Tetroxide–Periodic Acid Cleavage of Cholestane-3β-ol Tiglate.—To a stirred solution of cholestane-3β-ol tiglate (0.500 g., m.p. 106–108°) in dioxane (50 ml.) and water (3 ml.) was added osmium tetroxide (30 mg.) followed by periodic acid (0.910 g.). After 10 min., the precipitate which formed was dissolved by addition of water (5 ml.). The reaction mixture was stirred for 3 hr. and evaporated to dryness under reduced pressure. The residue was suspended in water (50 ml.) and extracted with chloroform, which yielded a white solid upon evaporation. The solid was dissolved in dioxane (200 ml.) and water (20 ml.) containing sodium bicarbonate (0.200 g.); the solution was brought to pH 8.5 by addition of dilute sodium hydroxide and allowed to stand overnight at room temperature. Evaporation to dryness under reduced pressure and extraction of the residue with chloroform gave a white solid (0.412 g.). Crystallization from ethyl acetate yielded cholestane-3β-ol (0.384 g., 89%), m.p. 141–143° (reported m.p., 142–143°[21].

Osmium Tetroxide–Periodic Acid Cleavage of *p*-Bromobenzoylcarbinol Tiglate.—*p*-Bromobenzoylcarbinol tiglate[22] (0.500 g., m.p. 67–68°) was treated according to the procedure described for *p*-nitrobenzyl tiglate. The crude reaction product was extracted with chloroform. Evaporation to dryness left a solid which was crystallized from ethanol to yield *p*-bromobenzoylcarbinol (0.285 g., 79%), m.p. 137–138° (reported m.p., 136.6°[23]).

Strophanthidol 19-Acetate.—A solution of strophanthidol[24] (V, 0.100 g., m.p. 138–142°) in pyridine (1.0 ml.) was treated with acetic anhydride (1.0 ml.) and the solution was allowed to stand for 45 min. at room temperature. The solution was then cooled in an ice bath, and methanol was added dropwise to destroy the excess acetic anhydride. Evaporation to dryness left a resin which was crystallized from acetone–ether (first crop, 30 mg., m.p. 135–140°; second crop, 29 mg., m.p. 130–135°). Both fractions appeared to be practically homogeneous on the basis of their behavior upon thin layer chromatography.[25] The R_f of the substance was distinctly lower than that of strophanthidol 3-acetate.[13] Recrystallization from acetone–ether gave crystals of m.p. 134–136°, $[\alpha]^{24}D$ +33° (*c* 1.01, chloroform).

Anal. Calcd. for $C_{25}H_{36}O_7 \cdot H_2O$: C, 64.36; H, 8.21. Found: C, 64.74; H, 7.99.

Strophthanthidol 19-Tiglate (VI).—Tigloyl chloride (0.23 ml.) was added dropwise to a cooled solution of strophanthidol (0.300 g., m.p. 138–142°) in pyridine (4.5 ml.). After 19 hr. at room temperature, methanol was added dropwise to decompose excess tigloyl chloride, and the solution was evaporated to a resin under reduced pressure. The resin was twice dissolved in benzene and evaporated to dryness to remove pyridine. The residue was dissolved in chloroform, washed twice with 2 *N* sodium carbonate, once with water, and dried over anhydrous sodium sulfate. Evaporation left a yellow oil which was chromatographed on neutral alumina (13 g. Woelm). The column yielded to 1 to 2% methanol in chloroform a resin (0.200 g.), $[\alpha]^{27}D$ +31° (*c* 1.11, chloroform); $\lambda_{max}^{chloroform}$ 2.90, 3.40, 5.60, 5.72, 5.88, 6.07, 6.17 μ.

Strophanthidol 3-Acetate 19-Triglate (VIII).—Strophanthidol 19-tiglate (VI. 0.200 g., $[\alpha]^{27}D$ + 31°) in pyridine (2.0 ml.) was treated with acetic anhydride (2.0 ml.), and the solution was allowed to stand at room temperature for 19 hr. Work-up in the usual manner gave a resin (0.201 g.), shown to have a preponderance of one compound by thin layer chromatography.[25] The material was chromatographed on neutral alumina (8 g., Woelm). The column yielded to 20 to 90% chloroform in benzene a resin (0.170 g.), $[\alpha]^{25}D$ −20° (*c* 1.42, chloroform): $\lambda_{max}^{chloroform}$ 2.80, 3.40, 5.60, 5.73, 5.87, 6.06, 6.17 μ.

Osmium Tetroxide–Periodic Acid Cleavage of Strophanthidol 3-Acetate 19-Tiglate (VIII).—To a stirred solution of strophanthidol 3-acetate 19-tiglate (0.170 g., $[\alpha]^{25}D$ −20°) in dioxane (15 ml.) and water (5 ml.) was added osmium tetroxide (8 mg.). After a few minutes, a black color developed. Periodic acid (0.175 g.) was added and the solution was stirred for 3 hr. at room temperature. The reaction mixture was treated with 0.1 *N* sodium arsenite solution, (100 ml.) and then with dilute sodium carbonate to pH 8.7. The solution was stirred for 30 min. and then extracted with chloroform. Evaporation to dryness left a solid (0.157 g.) which was shown to contain approximately 40% of unchanged starting material, by thin layer chromatography.[25] Consequently, the solid was again dissolved in dioxane–water and treated as above with osmium tetroxide (30 mg.) and periodic acid (0.243 g.). Workup as usual gave a pale yellow solid (0.132 g., 92%) shown to be homogeneous and to have the same R_f as an authentic sample of strophanthidol 3-acetate[13] by thin layer chromatography.[25] Crystallization from acetone–ether yielded colorless prisms (72 mg., 50%), m.p. 232–237°: $[\alpha]^{25}D$ +100° (*c* 1.25, chloroform). The infrared spectrum in chloroform solution was superimposable upon that of an authentic sample of strophanthidol 3-acetate (VII).

16-Dehydroprotoveratrin B 3′-Tiglate (XI).—A solution of protoveratrine B 3′-tiglate[16] (X, 0.758 g.) in glacial acetic acid (31 ml.) was treated with 0.066 *N* chromic acid in 99.8% acetic acid (46 ml.). Two-milliliter aliquots were withdrawn at appropriate time intervals and treated with 5% potassium iodide solution (5 ml.); the liberated iodine was then titrated with 0.01 *N* sodium thiosulfate solution in the usual manner. The titrations showed that oxygen equivalents of chromic acid consumed after 30 min. were 1.06; after 70 min., 1.27. After 80 min., the reaction mixture was cooled in ice and aqueous sodium bisulfite was added to destroy excess oxidizing agent. Dilute ammonium hydroxide was added until the solution was alkaline, and the alkaloid was extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to yield a resin (0.675 g.), which was shown to be homogeneous by paper

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(25) Merck Silica Gel G was used as adsorbent, methanol (8%)–chloroform as the developing solvent, and a saturated solution of 3,5-dinitrobenzoic acid in 2.8% potassium hydroxide in 50% methanol–water as spray reagent.

chromatography,[25] $[\alpha]^{25}D$ −24° (*c* 1.00, chloroform). Treatment of the product with alkali gave a substance which showed λ_{max}^{EtOH} 325 mμ and $\lambda_{max}^{0.1N\ NaOH}$ 377 mμ, characteristic of the diosphenol derived from 16-dehydroprotoverine derivatives.[16]

Sodium Borohydride Reduction of 16-Dehydroprotoveratrine B 3′-Tiglate (XI).—A solution of 16-dehydroprotoveratrine B 3′-tiglate (XI, 0.547 g., $[\alpha]^{25}D$ −24°) in *t*-butyl alcohol (50 ml.) was treated with sodium borohydride (0.126 g.). The mixture was allowed to stand, with occasional shaking, at room temperature for 30 min. The solution was acidified with acetic acid and evaporated nearly to dryness under reduced pressure. The residue was dissolved in water, made basic with dilute ammonium hydroxide, and extracted thoroughly with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was crystallized from ether (0.212 g.). Paper chromatography[26] showed that the crystalline product was inhomogeneous; a principal product with expected R_f was contaminated with other materials (probably partially hydrolyzed) with much lower R_f. Furthermore, the mother liquors contained only a mixture of the low R_f products. Chromatography of the crystalline mixture on Merck acid-washed alumina (42 g.) yielded to 50 to 80% chloroform–benzene, to chloroform, and to 0.5 to 1% methanol in chloroform a resin with R_f identical to that of protoveratrine B 3′-tiglate (X). Crystallization from acetone–ether yielded prisms (0.145 g.), m.p. 154–156°, with decomposition at *ca.* 173°; $[\alpha]^{29}D$ +10° (*c* 1.70, chloroform).

Anal. Calcd. for $C_{46}H_{69}O_{16}N$: C, 61.95; H, 7.74. Found: C, 61.95; H, 7.76. The melting point was not depressed by admixture of an authentic sample of protoveratrine B 3′-tiglate which had been crystallized from the same solvent, and the infrared spectra of the respective samples in chloroform solution were identical.

Osmium Tetroxide-Periodic Acid Cleavage of Protoveratrine B 3′-Tiglate (X).—To a stirred solution of protoveratrine B 3′-tiglate (X, 0.208 g.) in dioxane (30 ml.) and water (10 ml.) was added osmium tetroxide (15 mg.). After 10 min., a black color developed, whereupon periodic acid (0.232 g.) was added and the solution was stirred for 10 hr. at room temperature. The reaction mixture was treated with 0.1 *N* sodium arsenite solution containing a crystal of potassium iodide to pH 8.7, and stirred for 10 min. Extraction with chloroform and work-up by the usual procedure yielded a resin which was crystallized from acetone–ether to give prisms (0.113 g., 60%), m.p. 267–270° dec. The infrared spectrum in chloroform solution and the paper chromatographic behavior[26] were identical to those of an authentic sample of protoveratrine B.

(26) The paper chromatographic system was that of J. Levine and H. Fischbach [*J. Am. Pharm. Assoc.*, **44**, 543 (1955)]; *n*-butyl acetate–*n*-butanol–formic acid (25:5:1 by volume).

Chemistry of Dimethylketene Dimer. V. Reactions Involving Ester Anions[1]

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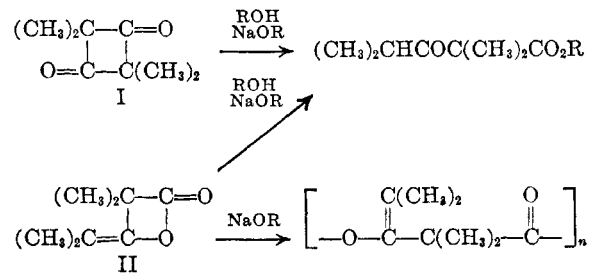
Received March 19, 1962

In the presence of a catalytic amount of sodium methoxide, the dimethylketene dimers (I and II) are disproportionated above 100° to the cyclic trimer, hexamethyl-1,3,5-cyclohexanetrione (V). The reaction involves the formation and acylation of the sodium enolate of methyl 2,2,4-trimethyl-3-oxovalerate. Various modes of preparing, alkylating, and acylating this sodium enolate are described.

The cleavage of tetramethyl-1,3-cyclobutanedione (dimethylketene dimer, I) by alcohols is catalyzed by basic reagents and leads to esters of 2,2,4-trimethyl-3-oxovaleric acid.[2] The β-lactone dimer of dimethylketene (II) is a more reactive acylating reagent than dimer I, but it also reacts sluggishly with alcohols unless a catalyst, preferably a base, is present. In the absence of active hydrogen compounds, the lactone dimer II, heated at moderate temperatures with sodium methoxide, is converted to a polyester; under the same conditions, dimer I does not react.[1]



When the reaction of the normal dimer I with sodium methoxide is forced by the use of higher temperatures, an exothermic disproportionation reaction takes place, and a high yield of the cyclic trimer, hexamethyl-1,3,5-cyclohexanetrione (V), is obtained.[3] Under these same conditions, the lactone dimer II, instead of polymerizing, is also converted to the cyclic trimer. It is evident that the two dimers react with sodium methoxide to form a common intermediate, the sodium enolate of methyl 2,2,4-trimethyl-3-oxovalerate (III).[4] The disproportionation of a dimethylketene dimer then involves the cleavage of another mole of dimer by the enolate III to generate the triketo ester anion IV. The cyclic trimer V is formed by an intramolecular attack of the nucleophilic center on the β-carbonyl group, with elimination of the methyl isobutyrate anion.

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