

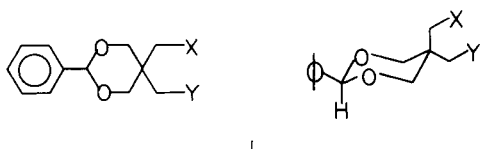
## Synthesis and Chemistry of 2-Phenyl-5,5-Disubstituted-1,3-Dioxanes (1)

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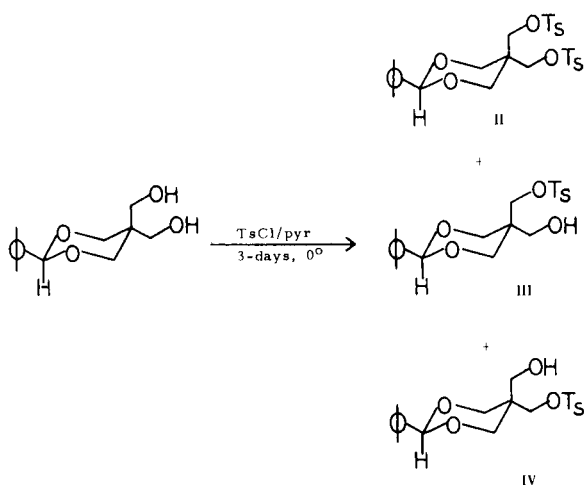
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The syntheses of functionalized 5,5-substituents of 2-phenyl-1,3-dioxane (1) has been accomplished, and the chemical procedures for obtaining mixed functionalities stereochemically has been developed.



The preparation of the dihalides of 1 ( $X = Y = \text{Br}$ , I) from the ditosylate (I,  $Y = X = \text{OTs}$ ) follows an apparent stereo-specific mechanism. The equatorial substituent at the 5-position is displaced in preference to the axial moiety affording the monosubstituted compounds as the major products (I,  $X = \text{OTs}$ ,  $Y = \text{Br}$ , I). The disubstituted compounds were always obtained as the minor products, and the axial displaced monosubstituents were never observed. Thin layer chromatography indicates that from the ditosylate, the dibromide and diiodide are formed by equatorial displacement followed by axial displacement. Unequivocal conformational assignments have been made by nmr spectroscopy and the spectral data are discussed elsewhere (2).

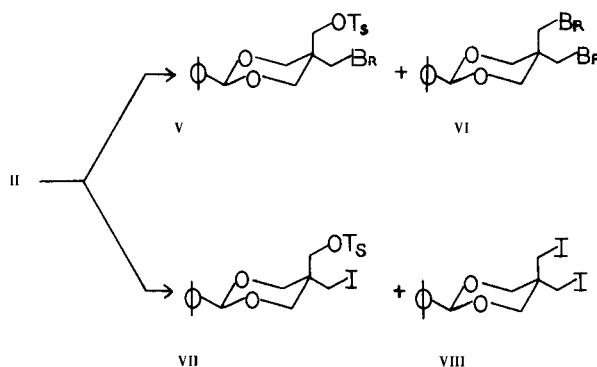
SCHEME 1



The ditosylate II was prepared from monobenzalpent-erythritol (3) (I,  $X = Y = \text{OH}$ ) by the method of Tipson (4) at 0 degrees in anhydrous pyridine. The best yield of II (Scheme 1) obtained was 87.6% at 72 hours. This procedure also yields products III and IV (Scheme 1).

Displacement reactions on the ditosylate II with sodium bromide or sodium iodide in different solvents and conditions yielded only two products: the equatorially displaced monosubstituted compounds V and VII and the disubstituted compounds VI and VIII (Scheme 2). When the ditosylate was heated at 95 degrees for 44 hours in the

SCHEME 2



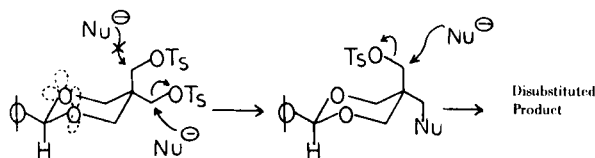
presence of sodium bromide in 2-methoxyethanol as a solvent, compound V, 2(e)-phenyl-5(e)-bromomethyl-5(a)-p-toluenesulfonylmethyl-1,3-dioxane, was obtained in a maximum yield of 84%.

Compound VII, 2(e)-phenyl-5(e)-iodomethyl-5(a)-p-toluenesulfonylmethyl-1,3-dioxane, was obtained in 83% yield by refluxing II in acetone (70 hours) with two equivalents of sodium iodide. Under all attempted conditions, the diiodo derivative VIII, 2-phenyl-5,5-bis(iodomethyl)-1,3-dioxane, was obtained in milligram amounts sufficient only for spectroscopic and elemental analyses. Compound VIII was isolated and purified by preparative thin-layer chromatography.

The tendency of these systems to be anomeric (2,5) aids in explaining the propensity for nucleophilic displacement of the equatorial tosylate in preference to the axial

moiety; because of the stereochemistry of these compounds (2,6,7), facile displacement of the axial moiety may be hindered electronically by repulsion of the nucleophile by the non-bonding electrons of the ring oxygens (Scheme 3). Displacement of the equatorial tosylate will decrease

SCHEME 3



the steric bulk around the axial 5-position, and after this first substitution, the distance between the groups may increase (8) thus allowing a second nucleophilic displacement. Another possibility is that axial displacement occurs subsequent to equatorial displacement *via* a chair-boat conformational equilibrium at the reaction temperature employed. This would be facilitated by the possible "planar" capability of the C<sub>4</sub>-C<sub>5</sub>-C<sub>6</sub> portion of the dioxane ring (6,7).

For comparison purposes, the dichloride (9) of 1 (X = Y = Cl) was prepared. The method of Wawzonek and Issidorides (9) also gave 3-phenyl-9-oxo-2,4,8,10-tetroxa-9-thiaspiro-[5.5]undecane as a minor product (I, X-Y = -O-S(=O)-). The dichloride was also prepared by the

procedure of Rapoport (10) using *p*-toluenesulfonyl chloride in refluxing pyridine (37.3% yield). In reactions of this type, the tosylate is postulated as the transient intermediate in the formation of the chloride derivative (4,11). Since the yields obtained of the dihalo derivatives are inversely related to their nucleophilicity, steric requirements must be minimal for displacement to occur at the C5 axial position. This is supported by the fact that essentially the same yields were obtained for the C-5 equatorial displacement (*i.e.*, V, 84%; VII, 83%).

#### EXPERIMENTAL

All melting points were determined in a Thomas Hoover Capillary melting point apparatus, and are uncorrected. The infrared spectra were obtained on a Perkin-Elmer Model 237 B Grating Spectrometer (potassium bromide), using a polystyrene film of 0.05 mm as reference. Nuclear magnetic resonance spectra were obtained on a Hitachi Perkin-Elmer R 20A at 60 MHz and are reported elsewhere (2). Thin-layer chromatography was performed on Brinkmann precoated aluminum sheets (Silica-Gel F-254) with layer thickness 0.25 mm. Preparative thin-layer chromatography was performed on 20 cm x 20 cm and 20 cm x 40 cm glass plates using Silica-Gel PF-254 at a 2 mm thickness. A Desage spreader and tank were used for application and developing. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

2-Phenyl-5,5-bis(chloromethyl)-1,3-dioxane (I, X = Y = Cl) and 3-Phenyl-9-oxo-2,4,8,10-tetroxa-9-thiaspiro[5.5]undecane (I, X-Y = -O-S(=O)-).

(a)

The method of Wawzonek and Issidorides (9) was used with minor modifications. The crude product after several recrystallizations from methanol afforded 57.2 g. (31.4%) of the desired dichloride I, (X = Y = Cl); m.p. 74-76°, lit (9) m.p. 77.5-78.5°; ir (potassium bromide) 3050-3030 (ArH), 2970, 2860 (CH<sub>2</sub>), 1498 (Ar), 1386 (CH<sub>2</sub>), 1310, 1295 (CH<sub>2</sub>Cl), 1110, 980 (C-O-C ring), 755, 705 (monosub Ar), 745, 735 cm<sup>-1</sup> (C-Cl).

A second product collected, m.p. 90-100° after several recrystallizations, twice from ethanol and twice from *n*-propanol, afforded 6.5 g. of a pure compound. The ir, nmr (2), and elemental analyses proved this latter compound to be I (X-Y = -O-S(=O)-); m.p. 114-116°

(previous softening); ir (potassium bromide) 2949, 2865 (CH<sub>2</sub>), 1499 (Ar), 1195, 1160 (sulfite), 1105, 970 (C-O-C ring), 765, 710 (monosub Ar), 690 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>5</sub>S: C, 53.33; H, 5.18; S, 11.86. Found: C, 53.68; H, 5.34; S, 11.60.

(b)

The method was patterned after that of Rapoport (10). To a cooled solution of 13.4 g. (0.07 mole) of *p*-toluenesulfonyl chloride in 30 ml. of dry pyridine, 7.84 g. (0.035 mole) of monobenzal-pentaerythritol (3) was added slowly with shaking. The temperature was kept below 5° for half of the addition, and between 15-20° for the remainder. The reaction mixture was refluxed for 12 hours, chilled in the refrigerator for several hours, and the resulting precipitate filtered by suction and washed with 5 ml. of dry pyridine. The combined filtrates were removed *in vacuo* and the residual magma worked up as reported. Recrystallization from a methanol-water solution yielded 3.4 g. (37.3%) of the dichloride (I, X = Y = Cl): m.p. 74-75°, lit (9) m.p. 77.5-78.5°; nmr and ir identical to that prepared by method a. Rapoport dried his compounds over sulfuric acid. However, this should be avoided with these compounds.

2-Phenyl-5,5-bis(*p*-toluenesulfonylmethyl)-1,3-dioxane (II); 2(*e*)-Phenyl-5(*e*)-hydroxymethyl-5(*a*)-*p*-toluenesulfonylmethyl-1,3-dioxane (III); and 2(*e*)-Phenyl-5(*a*)-hydroxymethyl-5(*e*)-*p*-toluenesulfonylmethyl-1,3-dioxane (IV).

Two hundred ml. of anhydrous pyridine was placed in a 1 l. Erlenmeyer flask which was fitted with a rubber stopper through which a thermometer was inserted. In the pyridine solution, 19.48 g. (0.087 mole) of monobenzal-pentaerythritol (3) was dissolved and the reaction mixture cooled to -10°. The solution was swirled by hand so as to keep the temperature below 0° and 36.50 g. (0.174 mole + 10% excess) of *p*-toluenesulfonyl chloride was added all at once. The reaction mixture was tightly stoppered and placed in the refrigerator freezer for three days, after which a voluminous precipitate had formed. The reaction mixture was placed in an ice-salt bath and 20 ml. of water (chilled to 0°) was added slowly in 5 ml. portions with constant agitation. This was followed by 175 ml. of water at the same temperature. At the end of the aqueous work up, the white solid mass was allowed to stand in the ice-salt bath for 1.5 hours, filtered by suction, and washed first with cold water (2 x 75 ml.) and then with cold methanol (2 x 50 ml.). The solid mass was dissolved in hot acetone, filtered, and concentrated with the addition of methanol, yielding 40.5 g. (87.6%)

of the ditosylate II; m.p. 176.5-177.0°; ir (potassium bromide) 3050 (ArH), 2850 (CH<sub>2</sub>, CH<sub>3</sub>), 1598 (Ar), 1365, 1200, 1180 (sulfonate ester), 1110-1105, 990-970 (C-O-C ring), 835, 820, 795 (*p*-sub Ar), 769, 705 (monosub Ar), 672 cm<sup>-1</sup> (C-S).

*Anal.* Calcd. for C<sub>26</sub>H<sub>28</sub>O<sub>8</sub>S<sub>2</sub>: C, 58.63; H, 5.29; S, 12.03; Found: C, 58.79; H, 5.40; S, 11.86.

The combined aqueous and methanol washings, were concentrated to obtain the monotosylated isomers III and IV. These derivatives were separated by fractional recrystallization from methanol.

Compound III; m.p. 126-127°; ir (potassium bromide) 3250 (OH), 3050 (ArH), 2960-2850 (CH<sub>2</sub>, CH<sub>3</sub>), 1597 (Ar), 1355, 1200, 1185 (sulfonate ester), 1110, 970 (C-O-C ring), 1049, 1030 (C-O prim. ROH), 921, 810, 805 (*p*-sub Ar), 760, 710 (monosub Ar), 695-679 cm<sup>-1</sup> (C-S).

*Anal.* Calcd. for C<sub>19</sub>H<sub>22</sub>O<sub>6</sub>S: C, 60.30; H, 5.85; S, 8.47; Found: C, 60.40; H, 6.00; S, 8.58.

Compound IV; m.p. 131.5-132.5°; ir (potassium bromide) 3490 (OH), 3050 (ArH), 2960-2860 (CH<sub>2</sub>, CH<sub>3</sub>), 1598 (Ar), 1365, 1198, 1185 (sulfonate ester), 1104, 975 (C-O-C ring), 1035 (C-O prim. ROH), 835, 820, 800, 791 (*p*-sub Ar), 761, 710 (monosub Ar), 672 cm<sup>-1</sup> (C-S).

*Anal.* Calcd. for C<sub>19</sub>H<sub>22</sub>O<sub>6</sub>S: C, 60.30; H, 5.85; S, 8.47; Found: C, 60.31; H, 5.97; S, 8.52.

2(e)-Phenyl-5(e)-bromomethyl-5(a)-*p*-toluenesulfonylmethyl-1,3-dioxane (V).

In a 50 ml. round bottom flask, fitted with a reflux condenser, 2.66 g. (0.005 mole) of II and 25 ml. of 2-methoxyethanol were heated to effect solution. Dry sodium bromide, 1.24 g. (0.01 mole, 20% excess), was added all at once, and the reaction mixture was maintained at 95° for 48 hours. The clear solution was cooled to room temperature and added to 150 ml. of water resulting in a flocculent precipitate. This was filtered by suction and dried affording 2.11 g. of a crude product, m.p. 134-139°. Recrystallization from an ethanol-acetone solution gave 1.85 g. (83.7%) of the monosubstituted compound V, m.p. 144.5-145.0°; ir (potassium bromide) 3027 (ArH), 2960, 2860 (CH<sub>2</sub>, CH<sub>3</sub>), 1593 (Ar), 1365-1355, 1190-1175 (sulfonate ester), 1250 (CH<sub>2</sub>Br), 1125, 990, 970 (C-O-C ring), 830, 820, 810 (*p*-sub Ar), 771, 709 (monosub Ar), 690 (C-Br), 670 cm<sup>-1</sup> (C-S).

*Anal.* Calcd. for C<sub>19</sub>H<sub>21</sub>O<sub>5</sub>BrS: C, 51.70; H, 4.79; Br, 18.10; S, 7.26; Found: C, 51.92; H, 4.89; Br, 18.19; S, 7.43.

2-Phenyl-5,5-bis(bromomethyl)-1,3-dioxane (VI).

Essentially the same procedure for the preparation of V was employed. In addition, 6-8 drops of diethylamine was added and the residual solution refluxed for 44 hours. The mixture was cooled to room temperature and stirred for 1.5 hours. The reaction mixture was added to 250 ml. of water (strong odor of benzaldehyde) and the aqueous solution extracted with chloroform (3 x 120 ml.) and then with ether (2 x 100 ml.). The extracts were dried (sodium sulfate) and removed *in vacuo*. The residual material proved to be primarily benzaldehyde (nmr, ir). The magma was dissolved in ether, washed several times with a sodium bisulfite solution, dried (magnesium sulfate) and the ether removed *in vacuo*. The resulting solid, 760 mg. (21.4%) m.p. 68-70°, proved to be the desired dibromide VI. Recrystallization from 95% ethanol afforded the analytical sample, m.p. 70-71°; ir (potassium bromide) 3050, 3025, 3010 (ArH), 2960, 2860, 2825 (CH<sub>2</sub>), 1593, 1460, 1450 (Ar), 1279, 1260, 1245 (CH<sub>2</sub>Br), 1125, 970 (C-O-C ring), 750, 700 (monosub Ar), 689, 670 cm<sup>-1</sup> (C-Br).

*Anal.* Calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>Br<sub>2</sub>: C, 41.17; H, 4.03; Br, 45.65; Found: C, 41.45; H, 4.19; Br, 45.58.

2(e)-Phenyl-5(e)-iodomethyl-5(a)-*p*-toluenesulfonylmethyl-1,3-dioxane (VII); and 2-Phenyl-5,5-bis(iodomethyl)-1,3-dioxane (VIII).

In a 100 ml. round bottom flask, fitted with a reflux condenser and a calcium chloride drying tube, 10.65 g. (0.02 mole) of II was added to 40 ml. of sodium iodide acetone solution (1.5 g. per 10 ml.; 0.04 mole) and the reaction mixture refluxed for 70 hours. The course of the reaction was followed by thin-layer chromatography (ligroin-ethyl acetate 2:1). After 24 hours, tlc showed trace amounts of diiodide, intermediate amounts of the tosylate iodide, with the major component being the ditosylate. After 48 hours the major product was the tosylate iodide. After 70 hours the reaction was discontinued. The solution was cooled to room temperature, and a white precipitate, which was filtered by suction, amounted to 4 g. of sodium *p*-toluenesulfonate. The solvent was removed *in vacuo* yielding a crude product. Recrystallization from 95% ethanol (Norit) afforded a first and second crop, 8.12 g. (83%), of the desired tosylate-iodide (VII): m.p. 119.5-120.5°; ir (potassium bromide) 3035 (ArH), 2970, 2850 (CH<sub>2</sub>), 1596 (Ar), 1355, 1195, 1185 (sulfonate ester), 1225 (CH<sub>2</sub>I), 1110, 1100, 975 (C-O-C ring), 822, 800 (*p*-sub Ar), 769, 709 (monosub Ar), 675 cm<sup>-1</sup> (C-S).

*Anal.* Calcd. for C<sub>19</sub>H<sub>21</sub>O<sub>5</sub>IS: C, 46.73; H, 4.33; I, 25.98; S, 6.56; Found: C, 46.66; H, 4.43; I, 26.02; S, 6.60.

The residual ethanol solution was added to 100 ml. of water, extracted with chloroform (3 x 75 ml.), and the resulting pink solution treated with *Norit*. The clear solution, after filtering through anhydrous magnesium sulfate, showed the presence of the diiodide when subjected to thin-layer chromatography. The position was compared to the dichloride, dibromide, and other analogs. Preparative thin-layer chromatography (ligroin-ethyl acetate 2:1) followed by Soxhlet extraction (24-36 hours; acetone) afforded VIII, m.p. 66.5-67.5°; ir (potassium bromide) 3020 (ArH), 1232 (CH<sub>2</sub>I), 1115, 980 (C-O-C ring), 755, 705 cm<sup>-1</sup> (monosub Ar).

*Anal.* Calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>I<sub>2</sub>: C, 32.45; H, 3.17; I, 57.15; Found: C, 32.67; H, 3.34; I, 56.99.

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