

THE SYNTHESIS OF 1,4-DIHYDROXY- AND 1,4-DIHALOGENOBICYCLO[2.2.2]OCTANES

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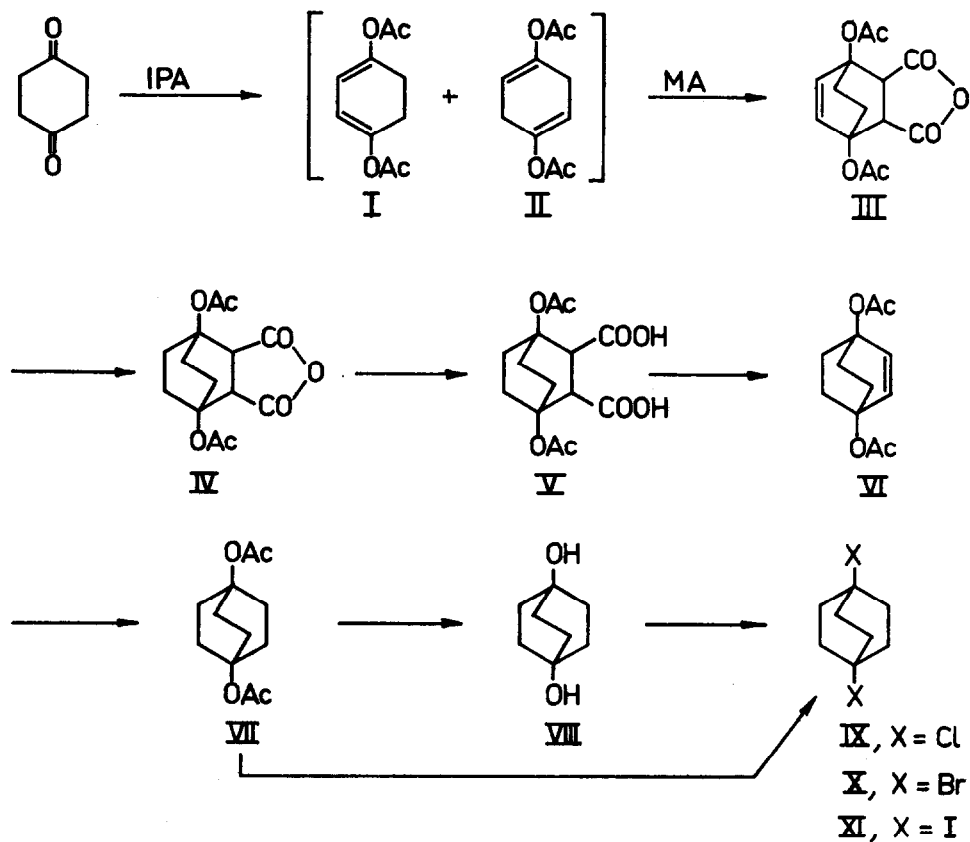
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Recently we reported a new method for the substitution of an hydroxy- or methoxy-group on the bridgehead carbon atom in the bicyclo[2.2.2]octane series by halogens (1), using various halogenating agents [e.g. POCl_3 , SOCl_2 , PBr_3 and also alkali chlorides, bromides or iodides (2)] in the presence of polyphosphoric acid (PPA). We wish now to describe a facile new synthesis of 1,4-dihydroxybicyclo[2.2.2]octane together with an extension of the halogenation reaction to the substitution of both hydroxy- or acetoxy-groups by halogens on bridgehead atoms, represented by the preparation of 1,4-dihalogenobicyclo[2.2.2]octanes.

The acid-catalyzed reaction of isopropenyl acetate (IPA) with 1,4-cyclohexanedione [forming a mixture of 1,4-diacetoxycyclohexa-1,3-diene (I) and 1,4-diacetoxycyclohexa-1,4-diene (II)] in the presence of maleic anhydride (MA) resulted in trapping of I as the Diels-Alder adduct, 1,4-diacetoxybicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (III)* in 50 - 55 % yield, m.p. 210-211.5° (benzene). Hydrogenation with Adams catalyst at atmospheric pressure in tetrahydrofuran gave 1,4-diacetoxybicyclo[2.2.2]octane-2,3-dicarboxylic acid anhydride (IV), m.p. 184-185.5° (acetone), in 99 % yield, which upon hydrolysis in 20 % aqueous potassium hydrogen carbonate and subsequent acidification with hydrochloric acid resulted in 94 % yield of 1,4-diacetoxybicyclo[2.2.2]octane-2,3-dicarboxylic acid (V), m.p. 189.5-190°

*) Satisfactory elemental analyses and consistent infrared and n.m.r. spectra were obtained for all compounds reported herein.



(50 % aq. acetic acid). The oxidative decarboxylation of the dicarboxylic acid with lead tetraacetate in a mixture of pyridine and acetonitrile (3) afforded 1,4-diacetoxycyclo[2.2.2]oct-2-ene (VI) in 49 % yield, m.p. 85-87° (sublimed at 80°/10 mm). Hydrogenation of this olefinic compound, under the same conditions as were employed with III, gave 1,4-diacetoxycyclo[2.2.2]octane (VII), m.p. 91-93° (sublimed at 90°/10 mm), in 99 % yield. The diester was hydrolyzed with sodium hydroxide to the known 1,4-dihydroxycyclo[2.2.2]octane (VIII) in 70 % yield (4).

Both the diacetoxycyclo- (VII) and the dihydroxycyclo- (VIII) compounds can be converted to the corresponding 1,4-dihalogenocyclo[2.2.2]octanes (IX - XI) by

the method described previously (1). When VIII was treated with an excess of phosphorus oxychloride in the presence of PPA, 1,4-dichlorobicyclo[2.2.2]octane (IX), m.p. 234-235° [lit. 233.5-234.5° (4) and 239-240° (5)], was obtained in 70 % yield. 1,4-Dibromobicyclo[2.2.2]octane (X), m.p. 256-258° [lit. 256.6-258° (4)], was formed in 66 % yield by the treatment of VII with an excess of phosphorus tribromide in the presence of PPA. The reaction of VIII with potassium iodide and PPA gave in 74 % yield the diiodobicyclo[2.2.2]octane (XI), m.p. 245-246° [lit. 245-246° (4)].

Further studies intended to exploit this halogenation procedure, especially those directed toward the preparation of 1-hydroxy-4-halogeno- and mixed 1,4-dihalogenobicyclo[2.2.2]octanes, are being actively pursued.

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