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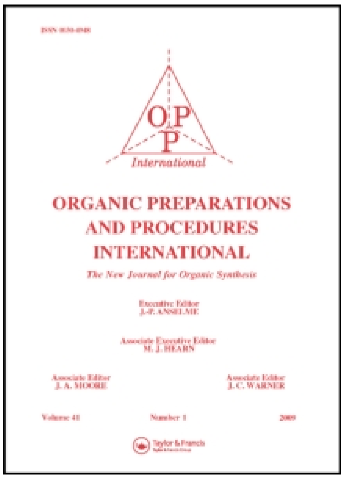

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PREPARATION OF 3, 6-EXO-OXO-HEXAHYDROPHTHALIDE

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ORGANIC PREPARATIONS AND PROCEDURES INT. 6(6), 265-267 (1974)

PREPARATION OF 3,6-EXO-OXO-HEXAHYDROPHTHALIDE**

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The lactone 3,6-exo-oxo-hexahydrophthalide III, a new compound, was prepared according to the scheme below.

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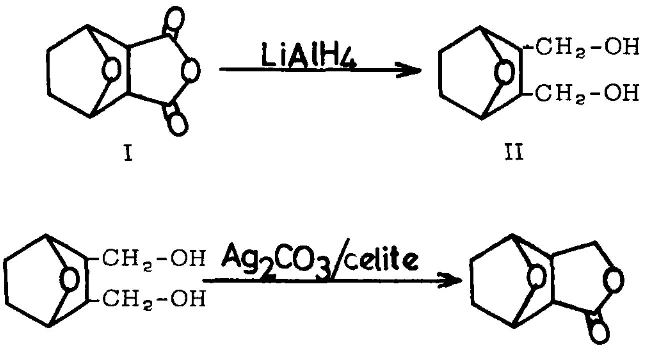

I II

II III

The exo stereochemistry which has been assigned[1] to the readily available starting material norcantaridine I is in accordance with our NMR data. Thus the NMR spectrum shows a multiplet at 1.75 ppm (4H) assigned to the methylene groups, a singlet at 3.2 ppm (2H) assigned to the protons alpha to the carbonyl groups and a multiplet at 4.99 ppm (2H) for the protons at the base of the oxygen bridge. The lack of an observable interaction between the alpha protons and those at the base of the oxygen bridge shows that the angle between them must be close to 90° corresponding to the exo-stereochemistry.

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Lithium aluminium hydride reduction of I yielded the di-alcohol II which was oxidized using the silver carbonate on Celite reagent described by Fetizon and his group.[2] All steps proceeded in reasonably good yields and the total yield of lactone III was about 60%. Refluxing p-xylene was found to be necessary to effect the oxidation step (boiling point 130° at 582 mm).

EXPERIMENTAL[3]

2,3-exo-dihidroxy methylene-7-oxabicyclo [2,2,1] hepane (II).- A solution of 8.8 g of 3,6-exo-oxo-hexahydrophthalic anhydride in 50 ml of peroxyde free THF was slowly added to a suspension of $LiAlH_4$ (in an amount equivalent to a two molar excess) in 100 ml of the same solvent. The mixture was stirred under reflux for five hours. After this period, the reaction mixture was externaly cooled with ice and a saturated sodium sulphate solution was slowly added with stirring until the reaction mixture turned white and no hydrogen was evolved. It was filtered and extracted with ethyl acetate (3 x 150 ml). A yellow liquid (8 g) was obtained and purified by column chromatography on silica gel, using ethyl acetate as eluent. The most polar fraction (6 g) was diol II, a solid mp. 55-57°. Molecular weight by mass spectrometry (m/e)140. The IR spectrum showed bands at 3630, 3420, 1095 and 1002 cm^{-1}. The NMR spectrum showed signals at (δ) 1.62 (m) and 2.15 (m) (6H), 3.66 (m, 4H) and 4.25 ppm (m, 2H) a broad multiplet at 3.00 ppm (2H) which disappeared upon addition of D_2O.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74 ; H, 8.92 ; O, 30.34.

Found : C, 60.80 ; H, 8.89 ; O, 30.04.

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3,6-exo-oxo-hexahydrophthalide (4,7-epoxyisobenzofuran-3-one) (III).- Diol II (5 g) was oxidized using the silver carbonate over Celite reagent (50 g) and p-xylene (400 ml) under reflux. Since the diol was not soluble in p-xylene, chloroform was used as a co-solvent which was gradually eliminated during reflux. After the reaction was completed (14 hours), the reagent was filtered and washed with a small amount of ethyl acetate. The product crystallized from acetone/hexane after purification by column chromatography on silica gel yielding lactone III, mp. 123-125° (85% yield). Molecular weight (m/e) 154 by mass spectrometry. IR 1760 and 1160 cm^{-1}. The NMR spectrum showed signals at (δ) 1.67 (m, 4H), 1.72 (m, 2H), 4.5 (m, 2H, ABX system), 4.51 and 4.83 ppm (m, 2H).

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.45; O, 31.14.
Found: C, 62.35; H, 6.40; O, 31.00.

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*To whom inquires should be addressed.

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1. R. B. Woodward and H. Baer. J.Amer.Chem.Soc., 70, 1161 (1948).

2. V. Balogh, M. Fetizon and M. Golvier. Angew.Chem.Inter. Ed. 8, 444 (1969).

3. IR spectra were obtained on a Perkin-Elmer 521 spectrophotometer. NMR spectra were determined on a Varian A 60A instrument. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6D mass spectrometer.

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