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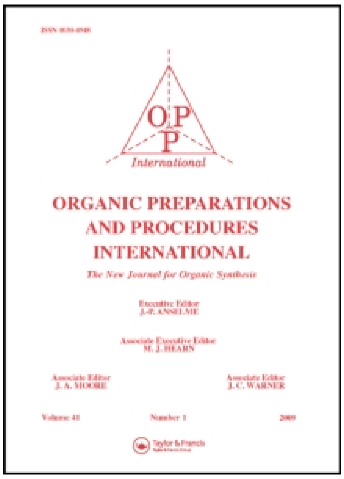

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A NEW SYNTHESIS OF 10, 11 -DIHYDRO-5H-DIBENZO (a, d)CYCLOHEPTEN-5-ONE

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A NEW SYNTHESIS OF 10,11-DIHYDRO-5H-DIBENZO (a,d)CYCLOHEPTEN-5-ONE

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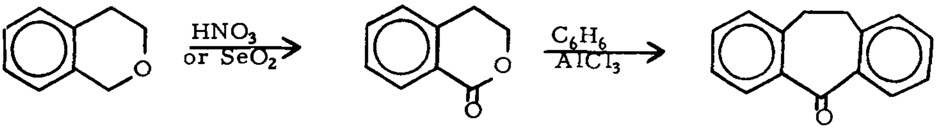

I II III

10,11-Dihydro-5H-dibenzo(a,d)cyclohepten-5-one(III) is a key intermediate in the synthesis of important psychotropic agents such as 5-(3'-dimethylaminopropylidene)-10,11-dihydro-5H-dibenzo(a,d)-cycloheptene (amitriptyline). The earlier method for its synthesis involved the condensation of phthalic anhydride with phenylacetic acid to give benzalphthalide, which was reduced with P-HI to 2-phenethylbenzoic acid.[1-5] Cyclization of the latter under a variety of conditions such as internal Friedel-Crafts,[2-4] treatment with phosphoric acid,[7] and polyphosphoric acid[5,6,8] gave (III) in over-all yields ranging from 30-52% for the three-step process.

Our interest[9] in Friedel-Crafts reactions of lactones with benzene and its derivatives led us to investigate a convenient one step synthesis of 10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5-one (III) from isochroman-1-one (II) and benzene in presence of anhydrous

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aluminum chloride. Since (II) is conveniently prepared by oxidation of isochroman with nitric acid or selenium dioxide, (III) can now be obtained in an over-all yield of 66%, starting with 2-phenylethanol.

EXPERIMENTAL

Isochroman (I).[10] -- A strong stream of dry HCl gas was passed through a well cooled (5-10°) mixture of 2-phenylethanol (400 g) and trioxane (123 g), with stirring. After 2 hr, the ice bath was removed, stirring and passage of HCl gas was continued for an additional 6 hr, while the temperature was kept between 35-40°. Excess HCl gas was removed *in vacuo* and the mixture was basified by the addition of NaOH (164 g in 800 ml H_2O). The mixture was then refluxed for 2 hr, cooled in ice and extracted with ether (5 x 200 ml). The ethereal layer was washed with H_2O, dried ($MgSO_4$) and the solvent removed. Distillation under reduced pressure gave isochroman (92%) bp 72-75°/5 mm (Lit.[10] bp 87-88.5°/10 mm), n_D^{20} 1.5448 (Lit.[10] n_D^{20} 1.5450).

Isochroman-1-one (II).[11] -- A. Oxidation with Nitric Acid: Isochroman (30 g) was added dropwise during one hr to a well stirred solution of conc. HNO_3 (130 ml) and H_2O (30 ml) preheated to 60°; there was a copious evolution of nitrogen oxide. The reaction mixture was maintained at 60° for an additional 2 hr, cooled and diluted with H_2O (150 ml). The oily product was separated and the aqueous phase extracted with ether (2 x 100 ml), the combined organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue

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upon distillation under reduced pressure gave isochroman-1-one (68%) bp 143-45°/5 mm (Lit.[11] bp 112°/0.4 mm), η_D^{20} 1.5624 (Lit.[11] $\eta_D^{18.5}$ 1.5664).

B. Oxidation with Selenium Dioxide: Isochroman (13.4 g) was added dropwise to a stirred suspension of SeO_2 (6.6 g) in refluxing xylene (30 ml). Stirring and refluxing was continued for an additional 6 hr, after which the reaction mixture was cooled, the Se metal filtered off and xylene removed *in vacuo*. Distillation of the residue gave isochroman-1-one (82%) bp 144-46°/5 mm, 112-14°/0.5 mm, η_D^{20} 1.5623, η_D^{18} 1.5669.

10,11-Dihydro-5H-dibenzo(a,d)cyclohepten-5-one (III): -- Powdered anhydrous $AlCl_3$ (53.2 g) was added to a mixture of isochroman-1-one (II) (14.8 g) and dry benzene (150 ml), during a period of 1.5 hr, with efficient stirring. The reaction mixture was stirred for one additional hr at room temperature, heated on a steam bath for 12 hr, then cooled and decomposed with ice and HCl. The benzene layer was separated and the aqueous phase was extracted with benzene (3 x 50 ml). The combined benzene extracts were washed with 10% KOH (2 x 50 ml), followed by H_2O, dried ($MgSO_4$) and evaporated. The crude product was distilled under *vacuo* to give 10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5-one (87.5%) bp 190°/5 mm, 147-48°/0.3 mm (Lit.[4] bp 148°/0.3mm), which solidified on cooling to a crystalline mass, mp 34-35°. I.R. (neat), 6.11, 6.29, 6.96, 7.76, 8.05, 8.72, 9.07, 10.75 and 11.03 mμ.

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