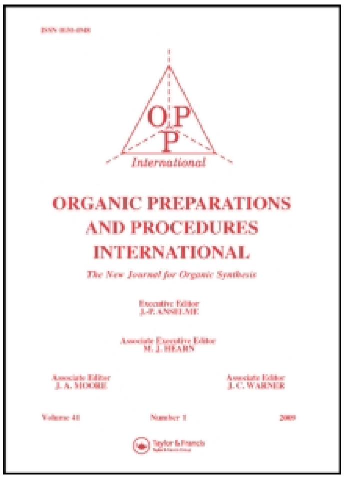

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A CONVENIENT NEW METHOD FOR THE PREPARATION OF DIMETHYL 3-METHOXYPHTHALATE

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A CONVENIENT NEW METHOD FOR THE PREPARATION OF DIMETHYL 3-METHOXYPHTHALATE*

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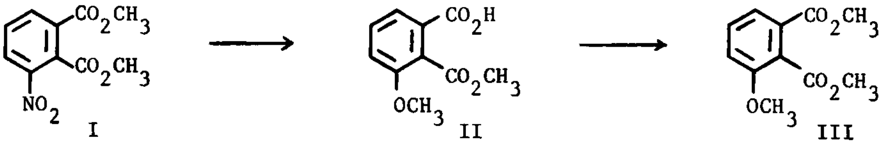
An essential reactant for many of the syntheses of adriamycin and related antitumor anthracycline antibiotics,[1] especially those with satisfactory regiospecificity,[2] is dimethyl 3-methoxyphthalate (III); this relatively simple chemical is however not commercially available. Although a number of syntheses of this and closely related substances has been reported,[3-21] these frequently fail to mention yields,[9-12] proceed in low yields,[7-9,11-14] are long, or utilize difficultly accessible starting materials. The best of these appears to be that of Eliel et al.,[10] although there is at least one instance of reported difficulty with it.[16] Rather than deal with a large scale diazotization reaction, we have chosen to employ a nucleophilic aromatic displacement reaction of an aromatic nitro group,[22,23] and find this sequence to be a convenient alternative to the Eliel method.



Thus, dimethyl 3-nitrophthalate (I) was smoothly converted to 2-carbomethoxy-3-methoxybenzoic acid (II) in 75% yield by stirring at room temperature with sodium methoxide in hexamethylphosphoramide solution for two days. The intermediate diester surprisingly easily undergoes partial saponification during aqueous work-up and of the two possible monoesters, II was proven to be the product by direct comparison with an authentic specimen.[24] The hydrolysis could neither be prevented by drowning the reaction in excess neutral phosphate buffer nor in cold, dilute HCl solution. While the ease of partial saponification may reflect a cryptic ring-chain tautomerism effect,[25] there is no present evidence which bears on this point and the resulting product is that which would result from attack on the least sterically hindered moiety. The synthesis of III was completed by quantitative reaction of acid II with diazomethane in Et_2O/MeOH or by Fischer esterification.

Thus, widely used anthracycline antitumor antibiotic synthon III is available in quantity from a commercially available starting material in two convenient, high yield steps.

EXPERIMENTAL SECTION

2-Carbomethoxy-3-methoxybenzoic Acid (II). - Dimethyl 3-nitrophthalate (4.8 g), either purchased commercially or prepared from commercial 3-nitrophthalic anhydride by refluxing with 5% conc. H_2SO_4 in MeOH solution, was added to a cold solution of sodium methoxide (2.61 g) in dry hexamethylphosphoramide (75 ml). The resulting dark solution was gradually brought to room temperature and the reaction mixture was stirred for 44 hr. It was then diluted with water (125 ml) and extracted with benzene. (This extract contained a variable quantity of dimethyl 3-methoxyphthalate (III).) The aqueous layer was acidified with HCl and extracted with benzene. The organic layers from extracting the acidified layer were combined and were washed three times with water, once with brine, then dried over sodium sulfate, filtered and evaporated to give 3.25 g (75%) of 2-carbomethoxy-3-methoxybenzoic acid, mp. 140-141°, lit.[24] mp. 141.5-143°. This material was spectroscopically and microanalytically pure and was used directly in the next step. Identity was confirmed by mixture mp., co-chromatography and spectroscopic comparison with an authentic sample.[24]

Dimethyl 3-Methoxyphthalate (III). - An ethereal solution of diazomethane generated from 21.0 g of Diazald® was reacted at ice-bath temperature with 14.9 g of II dissolved in MeOH. The excess diazomethane was decomposed with HOAc after a 15 min. room temperature reaction time. Evaporation of the solvent yielded 15.8 g (100%) of pure ester III, mp. 76-77°, lit.[7] mp. 73-74°; IR (KBr): 1740 cm^{-1}; pmr ($CDCl_3$): δ 3.80 (3H, s, $ArCO_2C\underline{H}_3$), 3.83 (3H, s, $ArCO_2C\underline{H}_3$), 3.90 (3H, s, $ArOC\underline{H}_3$), 6.97 (1H, d,d; J = 2, 8Hz, $Ar\underline{H}^4$), 7.25 (1H, t; J = 8Hz, $Ar\underline{H}^5$), 7.45 (1H, d,d; J = 2, 8Hz, $Ar\underline{H}^6$); eims m/e: 224 (M^+).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.39. Found: C, 58.85; H, 5.41.

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