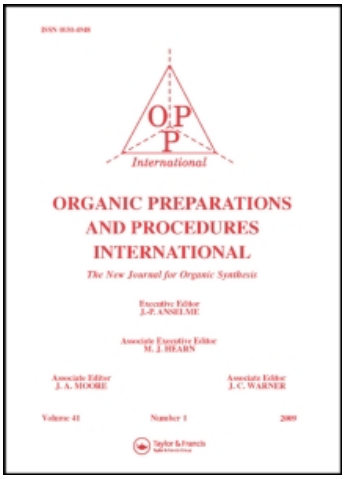

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF 2,6-DIMETHYLANILINE-^{14}C

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To cite this Article Middlebrook, Robert E. and Harvey, George R.(1969) 'SYNTHESIS OF 2,6-DIMETHYLANILINE-^{14}C', Organic Preparations and Procedures International, 1: 3, 165 — 170
To link to this Article: DOI: 10.1080/00304946909458373
URL: http://dx.doi.org/10.1080/00304946909458373

ORGANIC PREPARATIONS AND PROCEDURES 1(3), 165-170 (1969)

SYNTHESIS OF 2,6-DIMETHYLANILINE-^{14}C

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Current metabolism studies in this laboratory required ^{14}C ring labeled 2,6-dimethylaniline as the starting material for preparation of a pre-emergent herbicide. The literature disclosed several limitations associated with various preparations of 2,6-dimethylaniline. Low overall yields[1,2], unfavorable isomer distribution in direct nitration[3,4], and unavailability of labeled starting materials[5,6], rendered established synthetic sequences unsuitable for a radiosynthesis.

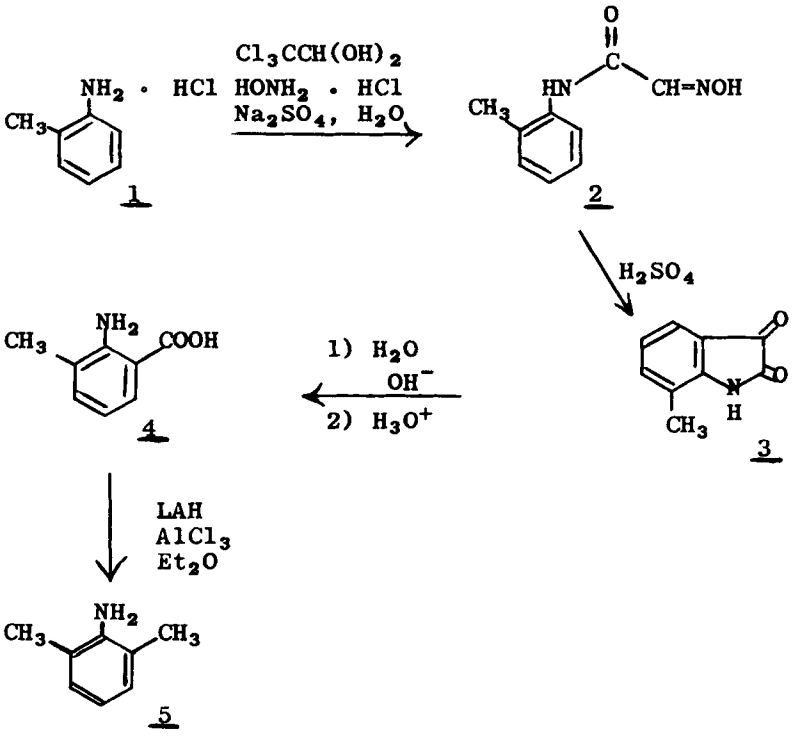
It appeared that the carbon skeleton could be readily derived by the preparation of 3-methyl anthranilic acid. Conversion of this acid to the desired 2,6-dimethylaniline could then be effected by reduction of the carboxyl group.

A convenient route to 3-methyl anthranilic acid was indeed available by oxidative hydrolysis of 7-methyl isatin[7]. This compound itself may be obtained in excellent yield from o-toluidine by the procedure of Marvel[8]. The final step, reduction of the carboxyl function to a methyl group, was smoothly accomplished in one step by the action of lithium aluminum hydride-aluminum chloride in refluxing ether. This latter reaction, though somewhat unusual, apparently owes its success to the stabilizing effect provided by the election pair of the o-amino

nitrogen on the incipient carbonium ion generated in the hydrogenolysis[9].

The complete sequence, as depicted in Chart I, fulfills quite adequately the special demands encountered in a radiosynthesis. Of particular merit is the fact that no purification of an intermediate product is necessary. Each compound may be used as it is obtained, and indeed, in both cold and labeled runs, even the desired aniline emerged from the reduction in a state that permitted its immediate use without distillation. Moreover, it may be noted that most reaction times are brief and stepwise yields are good.

Chart I



The synthesis should lend itself quite generally to the preparation of a variety of o-methyl anilines. Alternatively, the intermediate acid could be converted to several derivatives or perhaps function as a site for the incorporation of ring side chains.

Experimental

All melting points are uncorrected. The nmr spectrum was measured in $CDCl_3$ using TMS as internal standard on a Varian A-60 instrument. GC analysis was performed on an F and M Scientific 402 flame detector instrument using a 6 foot column (5% Carbowax 4000 on Gas Chrome A). Mass spectral analysis was carried out on a CEC 104 (70 eV) instrument.

Isonitrosoaceto-o-toluidine-1-^{14}C (2).-To 12 ml of distilled water in a flask containing 1.7 ml of concentrated hydrochloric acid was added 2.14 g (0.02 mol) of o-toluidine-1-^{14}C (1). The flask was stoppered and its contents stirred at room temperature 2 hr. To a 500 ml flask fitted with condenser, thermometer, and magnetic stirrer, the following reagents were added in order: 3.86 g (0.23 mol) chloral hydrate in 51 ml of H_2O and 52 g of sodium sulfate (crystalline, anhydrous), and this mixture was stirred 10 min at room temperature. The aqueous solution of (1) was then added followed by 4.39 g (0.063 mol) of hydroxylamine hydrochloride in 20 ml of H_2O. The mixture was heated to 100° over 30 min with stirring, maintained at this temperature 1 min, and allowed to cool to room temperature. Three extractions with ethyl acetate, followed by thorough water washing and drying (sodium sulfate), afforded 3.9 g of (2) on removal of solvent. The yellowish brown solid was used without further purification.

7-Methyl isatin-8-^{14}C (3).-Previously prepared (2) in a 250 ml flask fitted with calcium chloride drying tube was chilled in an ice bath to 0° and cold, concentrated sulfuric acid (10 ml) added. The reaction flask was placed in a water bath at 45°, magnetic stirring commenced, and the temperature slowly increased over 45 min to 80° and maintained 10 min. When the reaction flask had cooled, small pieces of ice were added to the contents thus precipitating (3). The reddish brown solid was filtered, washed well with H_2O, and air dried. The yield was 2.89 g, 90% from (1). This compound prepared in cold runs and recrystallized from hot water (red needles) shows mp 267-269° (lit., 267°[7]). Confirmation of its identity was provided by mass spectral data (70 eV): M^+ 161, m/e 105 (loss of two carbon monoxide units).

3-Methyl anthranilic acid-2-^{14}C (4).-To a stirred solution of (3) dissolved in 15 ml of 20% aqueous sodium hydroxide in a 125 ml flask was added 2.3 g (0.067 mol) of 30% aqueous hydrogen peroxide. The solution was brought to reflux and held 10 min. The alkaline solution was then chilled in an ice bath to 0° and slowly acidified dropwise with cold 20% aqueous sulfuric acid to pH 7. Further dropwise acidification with glacial acetic acid to pH 6 precipitated (4). The acid was filtered, washed with a small volumn of cold water, and air dried affording 1.47 g of tan solid. An additional 0.3 g of acid was extracted from the aqueous filtrate with ethyl acetate. The yield was 67% from (3). Acid prepared in cold runs showed mp 170-172°, (lit.[7], 170°) and ranged to 72% in yield.

2,6-Dimethylaniline-1-^{14}C (5).-To a stirred solution of 200 ml of anhydrous ether in a 500 ml flask fitted with calcium chloride drying tube and chilled to 0° was added 9.5 g (71.4 mmol) of aluminum chloride. To this mixture was added 1.36 g (35.7 mmol) of lithium aluminum hydride followed by stirring 1 hr at 0°. Previously prepared (4) (12 mmol) in 10 ml anhydrous tetrahydrofuran was then added to the reducing medium and the contents refluxed 21 hr with continued stirring. The hydride mixture was decomposed by dropwise addition of 10 ml of 5% aqueous potassium hydroxide solution at 0°. The mixture was extracted three times with ether and the combined extracts washed thoroughly with H_2O. To the remaining aqueous solution was added 10 ml of 10% aqueous potassium hydroxide and the extraction process repeated. The extracts were dried several hours ($MgSO_4$) before removal of solvent. A light brown oil remained (1.47 g, 95%) which displayed a single peak on gc analysis having a retention time the same as that of authentic 2,6-dimethylaniline (4.5 min at a column temperature of 150°). Ir and nmr spectra of synthetic and authentic material were identical. A crystalline N-benzoyl derivative was prepared, mp 169-171° (lit.[10], 168°) showing no depression of melting point on admixture with authentic material.

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(Received March 11, 1969)