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Synthesis of a Biochemically Important Aldehyde, 3,4-Dihydroxyphenylacetaldehyde

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3,4-Dihydroxyphenylacetaldehyde (DOPAL) is an important precursor of the major brain metabolites of dopamine, 3,4-dihydroxyphenylacetic acid and 4-hydroxy-3-methoxyphenylacetic acid. A new method for the synthesis of DOPAL from piperonal is described. We report for the first time the physical and chemical characteristics of DOPAL. Its importance for research in Parkinson's disease and Alzheimer's disease is discussed.

INTRODUCTION

3,4-Dihydroxyphenylacetaldehyde (DOPAL) is formed by oxidative deamination of dopamine (DA) by monoamine oxidase (MAO) (*1*, *2*). In tissues this aldehyde is either enzymatically oxidized to 3,4-dihydroxyphenylacetic acid or reduced to 3,4-dihydroxyphenylethanol (DOPET) (*2*, *3*). The synthesis of DOPAL is important for several reasons (see Fig. 1). First, a standard will allow an accurate measurement in human and animal tissues. Second, the human brain, in a number of disorders such as Parkinson's disease and Alzheimer's disease, is studied primarily using postmortem tissue. Deficits in catecholamines, including DA, are thought to play a role in these disorders (*4*, *5*). DOPAL is the precursor of other major brain metabolites of DA, including 3,4-dihydroxyphenylacetic acid and 4-hydroxy-3-methoxyphenylacetic acid or homovanillic acid (*6*). Carlsson and Winblad (*7*) have suggested that in postmortem brain the sum of a catecholamine plus its major metabolites is a better index of the level of the catecholamine in brain at the time of death than the catecholamine alone. This is supported by the findings of Warsh *et al.* (*8*) that catecholamines are metabolized in the brain after death. The measurement of DOPAL will therefore contribute to a more accurate estimation of premortem levels of DA in postmortem human brain. In addition, because the enzymes involved in metabolism of DOPAL (aldehyde reductase, aldehyde dehydrogenase, and catechol-*O*-methyltransferase) either are in very low amounts (*9*) or are extraneuronal (*10–12*), DOPAL may be an index of the intraneuronal metabolism of newly formed DA (*13*).

Finally, DOPAL is the initial MAO-B metabolite of dopamine. Blashko (*1*) has suggested that aldehyde metabolites generated by the action of MAO on amines

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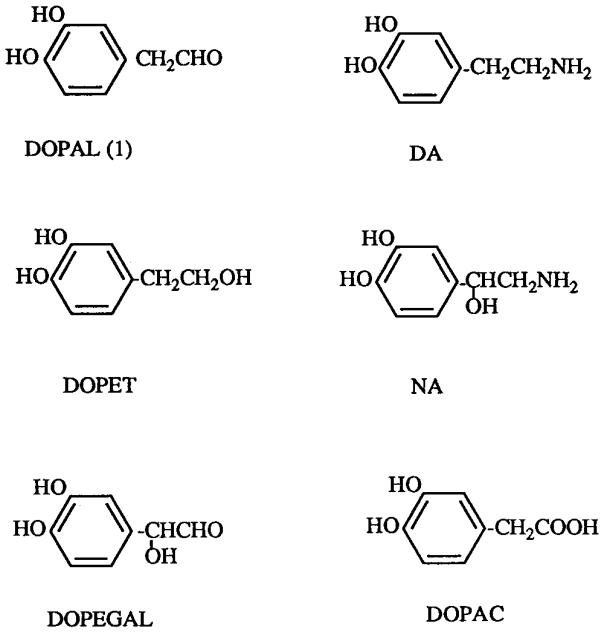
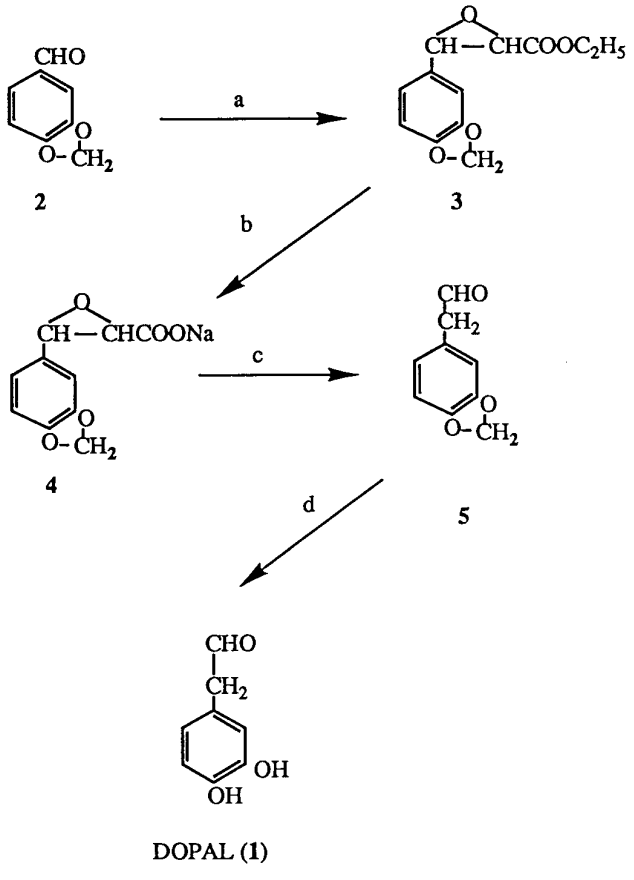


FIGURE 1

may be toxic to cells in which they are formed. Markey *et al.* (*14*) have shown that the exogenous toxin 1-methyl-4-phenyl-1,2,4,6-tetrahydropyridine, which causes a form of Parkinson's disease, becomes toxic to neurons only after its oxidation to the pyridinium form by MAO-B. We have previously synthesized 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL), the MAO-A metabolite of noradrenaline (NA) and adrenaline (*15*). DOPEGAL is a major NA metabolite in animal and postmortem human tissue (*16*, *17*). DOPEGAL, but not other noradrenaline metabolites, is toxic to cultured PC-12 cells (*18*) and triggers apoptotic cell death (*19*), the form of neuronal death found in Alzheimer's disease (*20*) and Parkinson's disease (*21*).

Attempts have been made to synthesize pure DOPAL (*22–25*). However, none of the methods provide detailed procedures and physical or chemical characterization of DOPAL other than its molecular weight by GC–MS. Such a method is important because, in order to study a potential role for DOPAL in neuron death in Alzheimer's disease and Parkinson's disease, it is necessary to develop a reliable method for synthesis and purification of large amounts of chemically pure DOPAL. The chemically pure compound is required for *in vitro* and *in vivo* tests of DOPAL toxicity as well as for quantification of DOPAL in brain neurons affected in Parkinson's disease and Alzheimer's disease (*21*, *26–28*).

In this paper we describe a new synthetic method for DOPAL and its physical characterization. The successful synthetic route uses commercially available piperonal as outlined in Scheme 1. Conversion of **2** to the ethyl glycidate (**3**) was accomplished by reaction with ethyl chloroacetate in the presence of sodium ethoxide.



SCHEME 1. (a) Ethyl chloroacetate, $NaOC_2H_5$; (b) NaOH, ethanol; (c) acetic acid, benzene; and (d) $BCl_3/S(CH_3)_2$, 1,2-dichloroethane.

Hydrolysis of **3** with sodium hydroxide gave the sodium salt (**4**) which upon treatment with acetic acid in benzene generated the aldehyde group to afford **5.** Final deprotection of the methylenedioxy group with boron trichloride–methyl sulfide complex gave crude **1,** which was purified by chromatography over silica gel.

EXPERIMENTAL

Melting points were determined on a Fisher–Johns melting point apparatus and uncorrected. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Gemini 300 spectrometer with Me_4Si as an internal standard. Field strength of various proton resonances is expressed as s, d, t, q, the center of which is given. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer.