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TELLURO AMINO ACIDS-SYNTHESIS, CHARACTERIZATION AND PROPERTIES OF A NEW AND POTENTIALLY USEFUL CLASS OF COMPOUNDS.

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The Te-123m nuclide emits 159 keV photons suggesting that agents labeled with this nuclide would be attractive candidates for tissue imaging. Amino acids labeled with Te-123m are of particular interest since some of these compounds would be isosteric with the sulfur analogs and might behave similarly in vivo. Such agents could possibly be useful for pancreatic imaging and for other biomedical applications. The goal of this investigation was to develop a general chemical method for the preparation of telluro amino acids. Attempts by other workers to prepare such compounds by microbiological methods have been unsuccessful (1). Since telluro amino acids were unknown prior to our studies we attempted the synthesis of a representative member of this class of compounds by several routes. Two general approaches were considered which involved either the introduction of an (organo telluro) 'reagent' into a 'substrate' that contained the protected $-CH(NH_2)COOH$ moiety or introduction of the 'reagent' into a 'substrate' that could subsequently be converted to the α-amino acid after the coupling step.

The feasibility of preparing telluro amino acids by several of the methods reported for the synthesis of seleno amino acids (2) was investigated. A pivotal step in many of these methods involves introduction of the (benzyl seleno) group as the 'reagent' species by reaction with various 'substrates.' This strategy involves the mild removal of the benzyl group with Na/NH_3 (du Vigneaud) followed by CH_3I methylation. The applicability of preparing telluro amino acids by these methods was studied. Benzyl tellurol ($Ph-CH_2-Te-H$) can be prepared from dibenzyl ditelluride but is very unstable. Attempts to introduce this moiety into a variety of amino acid substrates were unsuccessful. In fact, the facile decomposition of dibenzyl ditelluride in oxygen-free solvents was studied in detail by nuclear magnetic resonance spectroscopy. These results precluded the preparation of (benzyl telluro) intermediates which could serve as substrates for subsequent du Vigneaud reductive-methylation. Our extensive studies have thus clearly indicated that (benzyl tellurol) cannot be used for the synthesis of such compounds. Our early studies demonstrated the greater stability of compounds containing the (phenyl telluro) moiety (Ph-Te-R) compared to similar compounds containing (alkyl telluro) groups (R-Te-R'). For this reason model syntheses in which the (phenyl telluro) moiety was the 'reagent' were investigated.

One potential route that was conceived involved the coupling of (phenyl tellurol) (I) with (halo alkyl) substituted acetals. The preparation of β-(phenyl telluro) alanine (V) by this method (route 1) appeared particularly attractive since the crucial substrate, β-bromo-acetaldehyde dimethyl acetal (II), was available commercially. The strategy involved coupling of (I) and (II) to form β-(phenyl telluro)-acetaldehyde dimethyl acetal (III) with subsequent removal of the O-alkyl groups to yield the free aldehyde (IV) which could be subjected to a Strecker-type synthesis to form the telluro amino acid (V). The substituted acetal (III) was prepared in high

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yield (> 80%) and fully characterized. Unfortunately (III) was decomposed by acid treatment and the free aldehyde (IV) could not be obtained and this route was abandoned. Since the intermediate species such as (III) are formed in high yield it is conceivable that route 1 should be further investigated with a γ- or δ-halogenated acetal that would not be subject to facile β-elimination.

An alternate strategy involved the coupling of the 'reagent' to a 'substrate' containing the protected $-CH(NH_2)COOH$ moiety such as reaction of (I) with a 5-(halo alkyl) hydantoin (VI) (route 2). Selenomethionine was prepared sometime ago by such a route via a (benzyl seleno) hydantoin intermediate (3). We have found that modifications of this method can be used successfully to prepare telluro amino acids. Using the modified method the (telluro) substituted hydantoins yield the free (telluro) amino acids upon basic hydrolysis. We have prepared DL-α-amino-γ-(phenyl telluro) butyric acid (VII) as a model compound and DL-α-amino-γ-(methyl telluro) butyric acid (VIII, "telluromethionine") has also been prepared. More recently a variety of branched and α-alkylated compounds have been prepared. This "telluro hydantoin" method is a general route and the Te-123m labeled amino acids can also be prepared.

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