Reactions of Some Furanthione and Bithiophene Derivatives With a Study on the Isolation and Characterization of Some Stereoisomers

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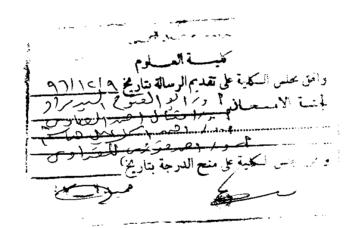
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List of Abbreviations

Ac acetyl

Ac2O acetic anhydride

Anal analysis

Bn Benzyl (PhCH2-)

8 Chemical shift in ppm relative to tetramethylsilane

DCC Dicyclohexylcarbodiimide

DMA N.N-dimethylacetamide

DMAP 4-Dimethylaminopyridine

DMF N.N-Dimethylformamide

DMFDMA dimethylformamide dimethylacetal

Et Ethyl

ether Diethyl ether

EtOAc Ethyl acetate

GC Capillary Gas Chromatography

GC/MS Gas Chromatography, Mass Spectrometry

h Hour

HPLC High Performance (pressure) Liquid Chromatography

HREI High Resolution (mass spectrometry). Electron impact lonization

IR Infrared spectroscopy

Jeoupling Spin-spin coupling constant (Hz)

LAH Lithium aluminum hydride

LAD Lithium alumium deuteride

L.R

Lawesson's reagent

LDA

Lithium diisopropylamine

I

litre

LRMS

Low resolution mass spectrometry

Me

Methyl

mmol

Millimole

MPLC

medium pressure liquid chromatography

n-BuLi

n-Butyllithium

 $NiCl_2dppp$

Bis(1,3-diphenylphosphino)propane nickel(II)chloride

NMR

Nuclear magnetic resonance spectroscopy

 P_2S_5

phosphorous pentasulfide

Рh

Phenyl

₽T

Room temperature

R

Rectus (configuration)

S

Sinister (configuration)

Τh

2.5-Disubstituted thiophene

THF

Tetrahydrofuran

TLC

Thin layer Chromatography

TMEDA

N.N.N'.N'-Tetramethylethylenediamine

 t_R

Retention time

ABSTRACT

Abstract

Abd El Sattar Sayed Ali Hamad

Reactions of Some Furanthione and Bithiophene Derivatives With A Study on the Isolation and Characterization of Some Stereoisomers. Doctor of philosophy of Science, Chemistry Department, Faculty of Science, Ain Shams University, 1996 The goal of the author is divided into three goals:

The first goal: Is related to the chemistry of furanthiones 72 and thiopyrrolines 73 which had recieved great attention in the last decades. The importance of this class of compounds stems from their facile ring opening. Besides, the bioligically active components are terpenoid in character which are components of nucleic acids and several types of unsaturated y-lactones of which ascorbic acid (Vitamin C) and useful chemotherapeutic agents (anti autoimmunity diseases). bactericide, and the thio-lactones have valuable effects on the growth of plants. 70,71 It was of interest to the author to try the conversion of some furanthioes 72 and thiopyrrolines 73 into heterocyclic systems of synthetic and biological importance viz. thioacrylic acid hydrazide 74. thiopyridazinone 75, thioacrylamide 77, and thiopyrroline-N-benzyl 78 derivatives. Second goal: Is related to the alkaloid chemistry of the michellamine A, B, and C analogs which are exciting new anti-HIV compounds and fully protective against HIV-1: The natural product michellamine $B(\mathbf{159})^{[7]}$ is an important compound with very promising anti-HIV properties and also are fully protective against both HIV-1 and HIV-2. Because of the promising anti-HIV profile of the michellamines, the preparation and evaluation of various analogs was of considerable interested. The preparation of a central binaphthol core of the natural product has been replaced by simpler 2.2'-bithiophene substructure as starting materials and as previously mentioned for the biological properties of bithiophene derivatives. A recent report showed that michellamine B inhibited enzymatic activities of reverse transcriptases from both HIV-1 and HIV-2. [33] It also inhibited cellular fusion and syncitium formation. Pharmacokinetic studies of michellamine B were also reported recently. 134 For this purpose our efforts are prompted toward the synthesis and

isolation of 2.2'-bithiophene-isoquinolines (241, 242, 252, 253), 2.2'-bithiophene derivatives

(249, 250, 251), and 2,2'-bithiophene-michellamine B analog (243) by using a palladium-mediated coupling reaction. But before we were able to undertake the synthetic challenges of bithiophene analogs, we suggested to study the synthesis and isolation of thiophene-isoquinoline (237, 238) derivatives as similituded.

Third goal: Is related to the food chemistry. The fungi are formed by bacteria parasitising in com, maize and other grains 234 and resist chemical treatment that is applied to the products in the food industry.²³⁵ In particular, 1,2,3-propanetricarboxylic acid (279) is found as a fragment in a number of natural product, such as mycotoxin fumonisin $B_1\ ({f 258})$ and a macrocyclic polycarboxylic acid which is inhibitor of Ras Farnesyl-Protein Transferase (FPTase), Actinoplanic acid A (296).²⁴¹ An unusual problem related to the determination of the absolute configuration of these fragments arose from the fact that 1.2,3-propanetricarboxylic acid itself is achiral, but being attached to the backbone with its pro-R or pro-S side, it becomes chiral. The 1.2.3propanetricarboxylic acid (PTCA) side chains are of particular interest in light of the observation 236 that hydrolyzed fumonisins not only retain biological activity despite having lost about half their molecular weight, but also have a broader spectrum of activity than the intact toxins. This observation has led to suggest that the producing fungi may enzymatically add PTCA moieties to the toxin backbone as a detoxification mechanism. This suggestions that the PTCA side chains are resistant to any chemical treatment of this fungus (Fumonisins and Toxins), led the author to become interested in determination of the stereochemistry of absolute configuration of 3-substituted $(\beta$ -Chiral) carboxylic acid and the information about the stereochemistry is important for biomedical studies of their activity. We used applications of NMR-based methods, utilizing various chiral auxiliaries, for establishing the absolute configuration of commonly encountered structural units β -Chiral acids (295) embody a structural unit that is of interest to us and for which no such method has been described.

Key Words: Furanthiones, Michellamine analogs, Fumonisins and A Convenient Method for Deterimination of Absolute Configuration of 3-Substituted (β-Chiral) Carboxylic Acids of side chain PTCA.