Synthesis and Characterization of 2(2-Tetrahydropyranylthio) methyl cyclopropylamine

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ABSTRACT

2(2-Tetrahydropyranylthio) methyl cyclopropyl amines were synthesized from allylmercaptan through several steps. The structures of the intermediates and the final products where confirmed through IR, NMR and elemental analysis, these compounds may be of value in the treatment of diseases where free radicals are implicated in their pathogensis, since the thio and the amino groups of the synthesized compounds may act as free radical scavengers.

الخـــــــــلاصة

لقد تم تحضير مجموعة من امينات الـ 2-(2-تتراهيدروبيران ثايو) مثيل سايكلو بروبيل من الليل ميركابتان وذلك من خلال عدد من الخطوات . تم تشخيص المركبات الوسطية والنهائية بواسطة تقنيه اشعة تحت الحمراء **(IR)** وطيف الرنين المغناطيسي **(H-NMR)** وتشخيص العناصر الاولية**(elemental analyses)** . هذه المركبات المحضرة ممكن ان تكون ذات قيمة في معالجة الامراض المتسببة من خلال تحرر الجذور الطليقة **(free radicals)**. لان وجود مجاميع الثايو والامينو في هذه المركبات ممكن ان تكون مهبطة لهذة الجذور الطليقة والمسببة للأمراض.

INTRODUCTION

Free radicals have been implicated in many diseases, among these are atherosclerosis, rheumatoid arthritis, cataracts, neoplastic diseass, diabetic retinopathy, Parkinson's, Alzheimer inflammatory diseases of gastro-intestinal tract and aging[1-5].

Free radicals are defined as atoms or molecules that contain one or more unpaired electrons and are species that cause metabolic disturbances and cell injury by interacting with macromolecules and other cellular constituents such as proteins, lipids, carbohydrates and DNA resulting in a variety of biological consequences, including cellular and tissue damage, mutation carcinogensis and cell death[6]. The observation that 2 - mercaptoethylamine , 2 –mercatopropylamine , disulfide ,

Thioethers and sulfoxides [7]were capable in protecting animals against free

radicals generated as a result of ionizing radiation promoted our interest to synthesize-2(2-tetrahydropyranylthio)

methylcyclopropylamine **1** . the thioether and the amino groups in 1 or the corresponding "sulfhydryl and amino groups in their expected major metabolites may act cooperatively as free radical scavengers".

Therefore these compounds may be utilized selectively to treat one or more of the previously mentioned diseases.

SYNTHETIC MATERIAL

Allylmercaptan , p- toluenesulfonic acid , dihydropyran ethldiazocetate , were obtained from Aldrich Chemical Co. (Milwaukee , WI ,USA) .

Analytical Equipment

Melting points were determinated by using a calibrated Thomas Hoover melting point apparatus .IR spectra were recorded using a Unicam SP- 300 spectrophotometer . NMR spectra were obtained using a Variant FT80A spectrometer. Chemical shifts are reported as part per million downfield from tetramethylsilane as internal standard for HNMR spectra . Elemental microanalysis were performed by H.Malissa and G.Reuter,FRG.

2- Allylthiotetrahyropyran (3) .

- Allylmercaptan (3,74g ,1 mole) and 200 mg of p-toluene sulfonic acid were placed in a 500ml RB- flask fitted with a reflux condenser and magnetic stirrer . Dihydropyran (84g , 1 mole) was added dropwise . The reaction mixture was heated on a steam bath for 10 minutes . After heating for 5-10 minutes , a vigorous exothermic reaction started and continued during the addition of dihydropyran . After 1 1/2 hours , refluxing was stopped and potassium carbonate (1.0 g) was added . The mixture was stirred at room temperature for 1 hour , filtered and fractionally distilled yielding 80.2 g .

(50%) of 2- allylthiotetrahydropyran (3) b.p . 42-44 (0.1 mm **)**

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Infrared (neat , cm^{-1}) showed bands at 3080 (= CH2, stretch); 2940, 2860 , 2850, (CH2, stretch); 1635 (C = C , stretch) ; 1180, 1080, 1040, 1015 (tetrahydropyranyl group) and 940 (S-CH2) Nmr (d- chloroform , δ) 1.28 - 2.18 (multiplet , 6 H , (CH2)3); 3.20 (multiplet , 2H, S-CH2) ; 4.09 and 3.5 (multiplEt , 2H , OCH2) ; The vinyl protons appear as multiplets overlapping with (O- CH-S) at 5.20 (multiplet , 3H , C=CH2 , O-CH-S) and 5.82 (multiplet , 1H , C=CH)

Anal . Calculated :Found for C8H14OS : C , 60.75 ;H , 8.86 ; S , 20.25 found : C , 60.63 ; H , 8.85 ; S , 20.47 .

Reaction of 2- allythiotetarhyropyran_ (3) with ethyl diazoacetate

In a 250 ml three - necked flask provided with a reflux condenser, dropping funnel and magnetic stirrer was placed 2-allythiotetraahydropyran (4,15.8 g , 0.1mole) and 50 mg of copper powder . The mixture was stirred rapidly (160 - 165 C° , oil bath) and the ethyl diazoacetate (11.4 g , 0.1) was added at such rate so as to avoid a vigorous reaction . After ethyl diazoacetate addition the evolution of nitrogen ceased . The reaction mixture was refluxed distillate (40-60 C° at 0.2 mm) . The distillate was analyzed by gas liquid partition chromatgraphy which shows the presence of several products . These products were tentatively identified as diethyl maleate , diethyl fumarate and the starting material . Other products are

a-

Ethyl α-allyl-α (2-_etrahydropyranythio) acetate (5) , b.p . 72-74 C°

at (0.015) mm , was identified by infrared and nmr spectra and elemental analysis . The infrared spectrum (neat , cm^{-1}) showed bands at 3080 (C=CH2 stretch); 2940 , 2860 , 2850 , (CH2- stretch); 1735 (C=O, stretch) ; 1640 (C=C) ; 1080 ,1050 , 1020 (CH2 , tetrahydropyranyl group) , 940 (S- CH2). Nmr (d- chloroform ,δ) , 5.78 (multiplet , 1H , HC=C) ; 5.24 (multiplet , 2H,C =CH2); 5.0 (multiplet ,1H,O- CH - S) ; 4.16 and 4.0 (multiplet ,3H ,COOCH2 , α- CHO of the (CH2 tetrahydropyranyl group) ;3.5 (multiplet , 2H , β__- CHO of the tetrahydropyranyl group ,S- CH -COOEt) , 2.57 (multiplet , 2H,CH2 - C=C) , 1.45 to 2.0 (broad , multiple ,6H (CH2)3) ; 1.25 (triplet , 3H, CH3)

Anal . Calculated: Found for C12H 20 O3S:C , 59 . 01/. ;H , 8.19; S, 13.11. Found : C,58.24 ;H,8.15; S,13. 45 .

b-

2(2-Tetrahydropyranylthio)methyl-1-carboethoxycyclopropane(4)

5.5g (22.5%), of 4,was obtained as a colorless liquid, b.p.120-122C° at (0.2mm). gas liquid partition chromatography on 3.8% silicon gum rubber (UC-W98) on chromosorb - W(80-100mesh), 4ft 0.25in glass column with column temperature 190C°, injection part temperature 320C°, detector temperature 280C°, inlet pressure of 40 psi and carrier gas (N2) flow rate of (60ml/min) showed two peaks at 3.2 minutes (87%) trans-4 and 4.0 minutes (13%) cis- 4.The mixture had an infrared spectrum (neat,cm^{-1}) that showed bands at 2900, 2860 (CH_2, stretch); 1720(C=O, stretch); 1105, 1080, 1040 and 1015 (tetrahydropyranyl group and cyclopropane absorption). NMR(d-chloroform ,δ)0.7-1.2(muliplet , 2H,CH2 of cyclopropane ;1.34(triplet, 3H, CH_3); 1.4-2.15(multiplet 7H$(CH_2)_3$, 1H of cyclopropane α to CH_2-S); 2.58 (doublet, 2H,S-CH_2,J-CH,CH_2-S = 6.5Hz) 3.3(multiplet, 1H, CH-cyclopropane α-to COOEt); 3.56(multiplet, 1H,β-CHO of tetrahydropyranyl group); 3.9(multiplet, 1H, α-CHO, of tetrahydropyrahyl group), 4.14(quartet, 2H,CH_2 of the ester group), 5.0(multiplet, 1H,O-CH-S).

Anal. Calculated: Found For $C_{12}H_{20}O_3S$: C ,59 .01H ,8.19 ; S ,13.11. Found: C,58.24;H,8.15;S,13.50

2(2-tetrahydropyranylthio) methylcyclopropylcarboxyhydr - azide(6)

A solution of (4.88g,$2.0x10^{-3}$mole) of 2-(2`-tetrahydropyranylthio)methyl-1-carboethoxycyclopropane 4 and 20 ml of 85% hydrazine hydrate was refluxed for 24 hours. The mixture was cooled and held at 0°C for 24 hours; no precipitate formed. The excess of hydrazine hydrate was removed under reduced pressure affording a semi-solid that failed to crystallize under various conditions. The unreacted ester 4 was removed by dissolving the crude hydrazide in chloform. The hydrazide 6 was precipitated with anhydrous ether. A white solid was obtained in Et_2O; this turned to a semi-solid upon removal of ether. The hyrazide 6 had an infrared spectrum (neat,cm-1) that showed bands at 3300 (NH_2, stretch) ;2920,2830(CH_2,stretch)1660(CONH, stretch); 1105 , 1080 ,1040 and 1020(tetrahydropyranyl group and cyclopropane ring). NMR (d-chloroform,δ)8.17(multiplet,1H,CONH) 4.97(multiplet,1H,O-CH-S); 4.05 and 3.55 (multiplet,2H,OCH_2) ;2.8-3.0 (multiplet , 3H ,

NH_2, CH -cyclopropane) ; 2.6 (multiplet , 2H , S-CH_2),1.1-1.2(multiplet,7H,$(CH_2)_3$ and 1H,CH-of cyclopropane α-to CH_2-S);0.8- 1.0 (multiplet,2H,$CH_2$of cycloprpane).
This semi-solid hydrazide was used without further purification.

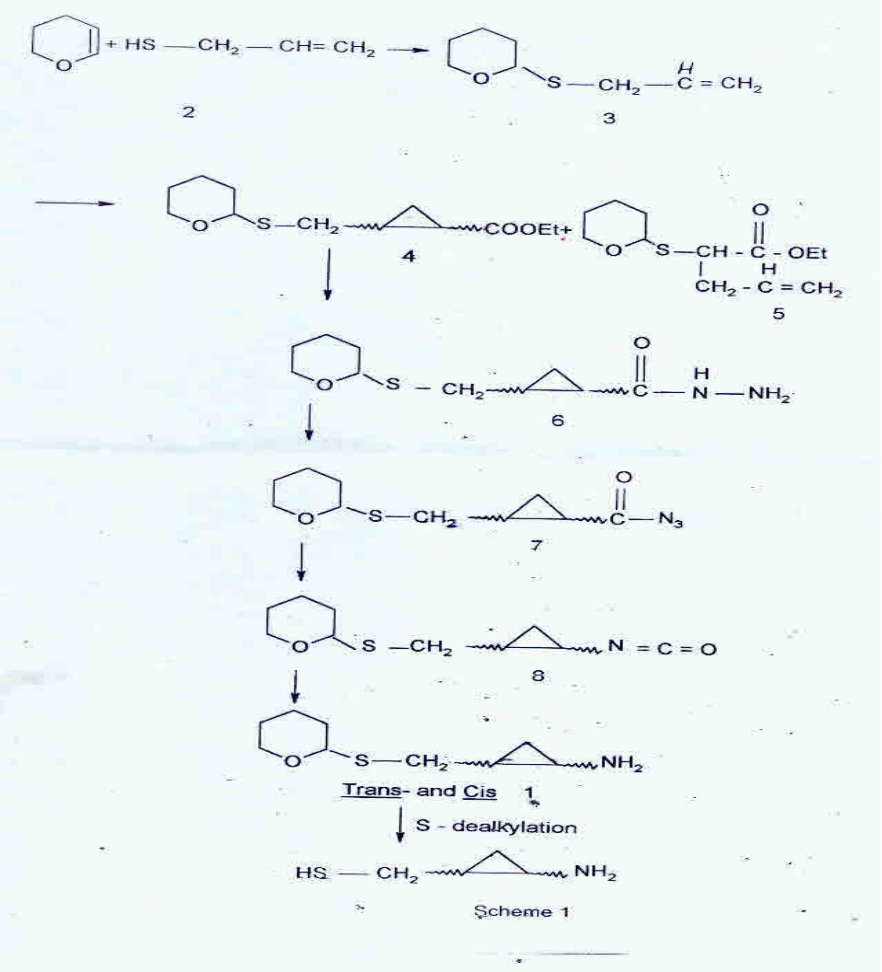
2(2Tetrahydropyranylthio)methylcyclopropylamin

A solution of (4.64g,$2.0x10^{-2}$mole) of 2- (2-tetrahydropyranylthio) methylcyclopropylcarboxyhydrazide 6 in 100ml chloroform was chilled to -5C°(ice-salt bath). With rapid stirring, 1.2g($2.0x10^{-2}$ mole) of sodium nitrite in 5ml of water, followed by 10ml of 10%HCl, were added. The reaction mixture was allowed to stand 5-10minutes; the chloroform layer was separated and the aqueous layer was extracted once with 20ml of chloroform. The combined chloroform fractions were dried (Na_2SO_4) and filtered. To this solution 50ml of dry toluene was added. The chloroform was removed under reduced pressure and N_2 evolution continued vigorously while heating the remaining toluene solution under reduced pressure on steam bath. After N_2 evolution ceased a dark brown solid material precipitated (infrared, KBr, $2280cm^{-1}$,N=C=O, 8). Fifteen ml of 25%methanolic KOH was added to the toluene containing the solid isocyanate and the mixture was refluxed at 125C° for 18 hours. After heating, the reddish brown mixture was extracted with toluene, dried (Na_2SO_4) filtered. The toluene was removed under reduced pressure. The residue was distilled affording 0.5g(26.7%) of cis- and trans-amine1,b.p. 98 -100C° at (0.3mm).Gass iquid partition chromatography (glpc)analysis on 3.8% silicon gum rubber (UC- W-98) on chromosorb – W (80-100 mesh), 4ftx0.25 in glass col temperature 175C°,injuction part temperature 300 C°and detector temperatur 285 C° inlet pressure 40 psi and carried gas (N2) flow rate of (60ml /min) showed two peaks at 1.28 minutes (85%) trans-1and 2.48 minutes (15%) cis-1.
The amine mixture had an infrared spectrum (neat,cm^{-1}) that showed bands at 3600-3300(broad, NH_2,stretch); 3000 , 29 30 and 2860 (CH_2,stretch) 1625-1590(NH,bending); 1105,1080,1045 and 1015 (tetrahydropyranyl and cyclopropyl ring). NMR (d-chloroform, δ) 4.97(multiplet ,1H , O-CH-S) ; 4.0 nd 3.5(multiplet,2H,O-CH_2); 2 .6 (multiplet, 2H , S-CH_2) 2.3 (multiplet, 1H , CH , cyclopropane α - to NH_2) ; 1 . 2-2 (multiplet,7H,$(CH_2)_3$,1H,CH cyclopropane α-to CH_2S) , 0.7 - 1.1 (multiplet ,2H ,CH_2 ,cycloprpane)

Anal. Calculated: Found For $C_9H_{17}OSN$:C,57.75,;H,9.09;N,7.48;S,17.11.
Found : C , 57 .19 ; H , 8 . 84 ;N,7.03;S,18.44.

RESULTS and DISUSSION

The new compound 1 was prepared as depicted in scheme 1 Allymercaptan 2 which serves as starting material was readily converted in 80% yield to 2-allylthiotetrahydropyran 3 through reaction with 2,3-dihydropyran in the presence of p-toluenesulfonic acid. The IR and NMR spectra were consistent with the assigned structure . Treatment of 3 with ethyldiazoacetate afforded a mixture of trans - and cis- 2-(2-tetrahydropyranylthio) methyl-1-carboethoxycyclopropane 4 and a sulfonium ylide rearrangement product namelyethyl-α-allyl-α (2-tetrahydropyranylthio) acetate 5 in 81.4% and 18.6% yield at 150-155C° respectively [8]. Ethyldiazoacetate reacts with allymercaptan to generate trans- and cis-cyclopropane derivative 4 through carbene addition to the double bond [9] and with thioether group to form sulfonium ylide [10]. Such sulfonium ylide is known to undergo Steven's rearrangement, which depends on the structure of the ylide, may either involve an antrafacial 1,3-sigmatropic rearrangement or suprafacial 1,5-sigmatropic rearrangement [11]. In our case both 1,3- and 1,5- rearrangements afforded the same compound 5. The mixture of 4 could not be separated by physical methods and was used as a mixture in the next step. Reaction of 4 with 85% hydrazine hydrate afforded the hydrazide 6 as a gummy solid in almost quantitative yield; Attempts to crystallize this gummy hydrazide were unsuccessful. The purity of the compound was determine by gass liquid partition chromatography (glpc); the non-crystalline hydrazide was then subjucted to Curtius rearrangement. The rearrangement proceeded through the azide 7 and the isocyanate 8. The intermediate azide 7 was detected by its IR spectrum (CON_3, 2150 cm^{-1}). The isocyanate 8 could be isolated as a brown solid which showed an IR absorption band at 2280 cm^{-1} (N=C=O). The isocyanate 8 was refluxed with 25% methanolic KOH to generate the desired trans- and cis- cyclopropylamine 1 as a mixture in a ratio of 85:15 respectively. The IR and NMR spectra were consistent with the assigned structure as discussed in the experimental part.



Scheme 1

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