Synthesis of Some Substituted Pyrano 1, 3-oxazine

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Abstract

7-Chloro-2- methyl thio-2-N-ethyl carbazato, 2N-acetyl tyrosyl hydrazido 4,5-dioxo pyrano [3, 4-e] - 1, 3-oxazine -4, 5-dione [2] , 2, 7-di(N-ethyl carbazato) 4,5-dioxo pyrano [3, 4-e] - 1, 3-Oxazine -4, 5-dione [3] and, 7- chloro 2N-acetyl amino acid hydrazido , 2N-benzoyl amino acid Hydrazido-4,5-dioxo pyrano [3, 4-e]-1,3-oxazine 4, 5-dione [4] were synthesized by standard methods. The pyrano -1, 3-oxazine [1] was prepared from condensation of two moles of malonyl chloride with methyl or benzyl thiocyanate. Spectroscopic characteristics (IR, NMR) of the pyrano -1, 3-oxazine derivatives are presented and discussed.

الخلاصة :

في هذا البحث تم تحضير المركبات ٧– كلورو– مثيل ثايو– 2-N- اثيل كاربازيتو ، 2-N- اسثيل تايروسيل هيدرازيدو–٥،٤– دايوكسوبايرانو [٤،٣–أي] - 1 ،٣– اوكسازين –٥،٤– دايون [٢] والمركب ٧،٢– ثنائي [N –اثيل كاربازيتو] –٥،٤– دايوكسو بايرانو [٤،٣–أي] – 1 ،٣– اوكسازين– ٥،٤– دايون [٣] والمركب ٧– كلورو–N2 – استيل هيدرازيد الحامض الاميني ، N2– بنزوايل هيدرازيد الحامض الاميني –٥،٤– دايوكسو بايرانو [٤،٣–أي] – 1، ٣–اوكسازاين ٥،٤– دايون [٤] هذا وقد حضرت تلك المركبات بالاعتماد على طريقة التحضير العامة . أما المركب يايرانو ٣،١–اوكسازين [١] فقد حضر من تكاثف مولين من كلوريد المالونيل مع مول واحد من ثايوسينات المثيل أو البنزيل وتم مناقشة أطياف المركبات المحضرة والمتمثلة بالـIR والـ^{1}HNMR .

Introduction:

Substantial number of 3,4-dihydro-1,3-2Hbenzoxazine derivatives were synthesized from the reaction of p-substituted phenol with dimethalol amines [1].

The condensation of naphtols with formaldehyde and primary amines was also used to the synthesis of 2,3-dihydro-2-substituted-1H naphtha[1,2-e[-1,3-oxazines or N,N-bis(2-hydroxy-1- naphthyl methylol amines[2] .Some dihydro-1,3-benz oxazines were studied and were found to have anti tumour activities[3]. Coppla and M.Gray prepared 2,3-indoline dione[4].This compound was used in the preparation of compounds having pharmacological activity which comprises reacting a 1,3-benzoxazine with an alkali or alkali earth metal cyanide to obtain 2- imino-3-indolino derivatives which then subjected to hydrolysis.

Number of 1,3-oxazine derivatives often have analgesic, anti-inflammatory and anti leukaemic activities[5-7]. Aminoacid ester derivatives of pyrano-1,3-oxazine becomes an area of interest due to their antibacterial or anti fungal activities[8,9]. Our interest in the synthesis and the biological study of (ethyl carbazato) derivative of pyrano-1,3-oxazine which was found to behave as anti cancer agent[10], brought great attention to study hydrazide as derivatives of pyrano-1,3-oxazine. In view that hydrazides themselves have been studied and were found to pocess anti bacterial, virul and anti fungal activities [11-14].

They also used as plant growth control [15].Recent study on 1,3-oxazine compounds includes; The synthesis of (RS)-3-tert-butoxycarbonyl-perhydro-1,3-oxazine-2-yl acetic acid and the synthesis of the simple and C-2 substituted 3-tert-butoxycarbonyl-perhydro-1,3-oxazine-2(RS)-yl propionic acids from simple starting materials[16] ,Streocontrolled synthesis of D- erythrosphinogosine and D-ribo-phytosphingsine which has a variety of physiological value [17],European patent for the production of photo chromatic pyrano1,3-oxazininonaphthalene derivatives[18],Synthesisof 7-chloro-3-substituted-3,4-dihydro-4,5-dioxo-2-thio-2H,5H-pyrano[3,4-e]1,3-oxazine[19],New approach to the synthesis of Biginellic compounds and their analogues[20] ,Synthesis and crystal structure study of 5-(4-methoxy benzyl)-6-(4-methoxyphenyl)-3-phenyl-2,4-dihydro-2H-1,3-oxazine-2,4-one[21].Among the biological values of 1,3-oxazine compounds are ; The studies of P.Kaylo,J.AL-Rawi and A.H Hugher for the production of some 1,3-benzoxazine derivatives from 2-(hydroxyl,thio or amino)aromatic acid using the triphosphinothiocyanogen reagent,The synthesized compounds were used as antiplatelete agent[22].The more recent study on the 1,3-oxazine compounds is the work of AL-Rawi and his coworkers on the synthesis of 2-(ethyl aminoacid estrers)-1,3-oxazine which has the ability to inhibit DNA-Dependent protein Kinase[23].

In this paper we describe an approach to the preparation of amio acid hydrazide derivatives of pyrano-l,3-oxazine . Our next work will be the biological study of the above synthesized compounds.

Experimental

Uncorrected melting points were determined using electrothermal 9300 melting point apparatus. I.R. spectra were recorded by Pye Unicam SP1100 Spectrophotometer as KBr disc. ^{1}HNMR spectra were measured with Hitachi 60 MHz spectrometer at Education college of Mosul University. 7-chloro-2-benzyl (or methyl) thio-4,5-dioxopyrano [3, 4-e] -1, 3-oxazine 4, 5-diones (la-b) were prepared according to the reported procedure [24] .

Preparation of amino acid ester hydrochloride[24]:

A stream of dry hydrogen chloride gas was passed rapidly through suspension prepared by dissolving 10 g. of amino acid in 150 ml of absolute ethanol, their melting points were determined and checked with the literature values.

Preparation of amino acid ester: [25]

A stream of dry ammonia gas was passed through suspension made by dissolving 10 gm. of amino acid ester hydrochloride in 100 ml. of dry methylene chloride. The ammonium chloride was filtered off, the solvent was evaporated under reduced pressure giving yellow color liquid.

Preparation of benzoyl (or acetyl) amino acid ester[26]:

To an ice cooled solution of 0.01 mole benzoyl chloride (or acetyl chloride) in 50 ml. dry dichloromethane was added drop-wise a solution of 0.02 mole of amino acid ester in 50 ml dichloromethane with stirring. After the addition has been completed, the reaction mixture was refluxed for 1 hr. cooled and washed with sodium bicarbonate solution (5%) then with water and dried. The melting points together with IR spectral data are presented in (Table 1).

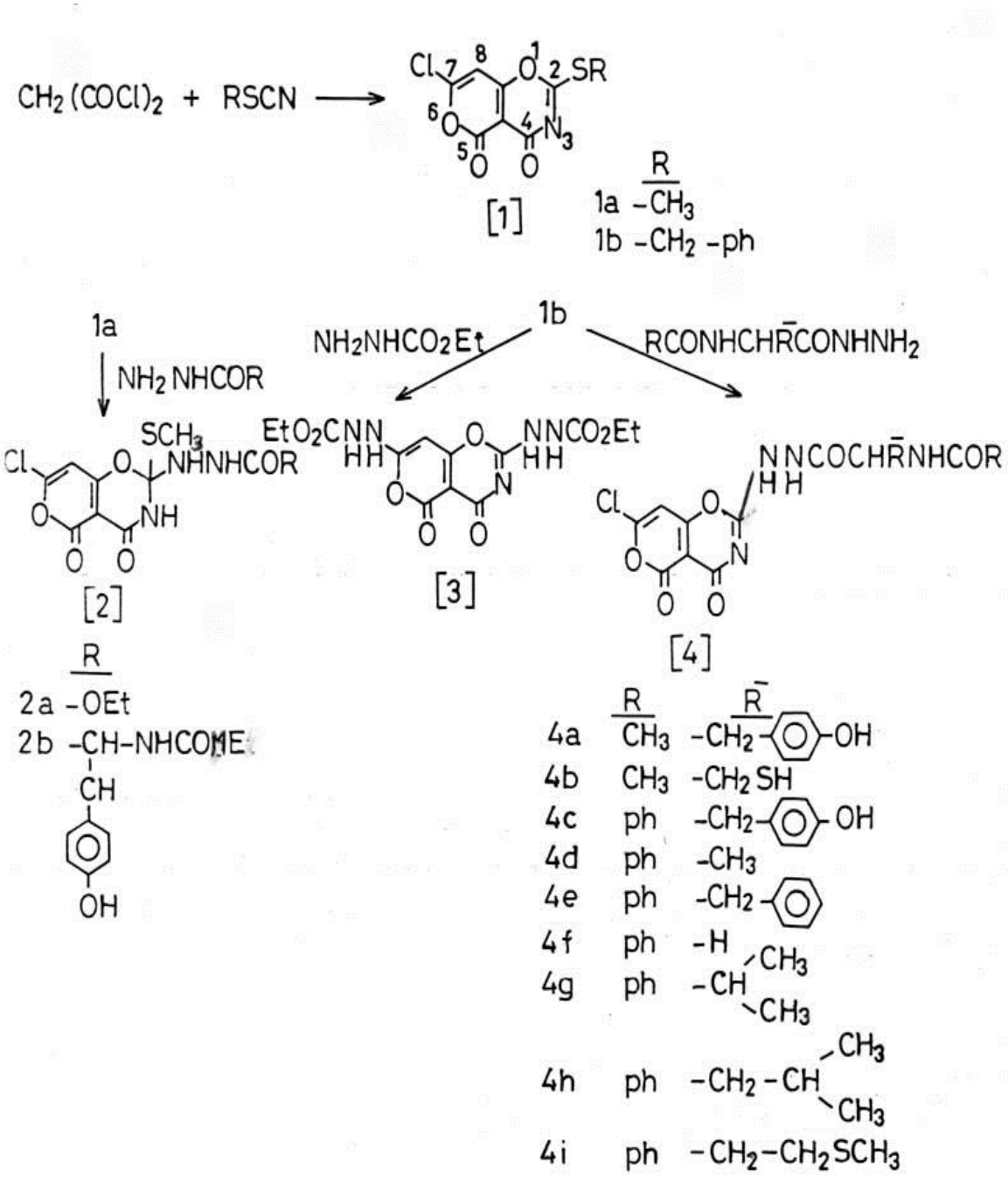
Preparation of benzoyl (or acetyl) amino acid hydrazide[27]:

A solution of 0.02 mole of benzoyl (or acetyl) amino acid ester and 0.01 of hydrazine hydrate in 50 ml. of absolute ethanol was refluxed for 1 hr. cooled, the precipitate was filtered off and recrystallized from ethanol. Physical and spectral data are illustrated in (Table 2).

Reaction of benzoyl and acetyl amino acid hydrazide with 2-benzylthio-7-chloro-4,5-dioxopyrano[3,4-e]-l,3-oxazine-4,5-dione; The synthesis ofcompounds (4a-i)[8]

In 100 ml. round bottomed flask fitted with reflux condenser and dropping funnel , was placed (0.01 mol) of compound (1) in 40 ml. of dry chloroform.

The reaction was carried on by dropwise addition of benzoyl (or acetyl) amino acid hydrazide (0.01 mole) in 20 ml dry chloroform through dropping funnel with continuous stirring. After completing the addition the reaction mixture was refluxed for 6 hr, cooled and the solvent was evaporated under reduced pressure. The solid crude product was then recrystallized. The spectral data of the synthesized compounds (4a-i) together with their physical constants are presented in Table (3).


CH2(COCl)2 + RSCN
[1]
R
1a –CH3
1b –CH2 –ph
1a
NH2NHCOR
1b
NH2NHCO2Et
RCONHCHR̄CONHNH2
[2]
[3]
[4]
R
2a –OEt
2b –CH–NHCOME
CH
OH
R R̄
4a CH3 –CH2 –OH
4b CH3 –CH2SH
4c ph –CH2 –OH
4d ph –CH3
4e ph –CH2
4f ph –H
4g ph –CH(CH3)2
4h ph –CH2–CH(CH3)2
4i ph –CH2–CH2SCH3

Scheme -1-

Table (1) : Amino acid esters IR spectral data together with their melting points.

Amino acid esters	C=O amide ν cm^{-1}	C=O ester νcm^{-1}	NH νcm^{-1}	M.P^{0}C
CH_3CO-tyr-OEt	1630	1735	3200	245
Ch_3CO-cys-OEt	1665	1740	3350	109-111
PhCO-tyr-OEt	1630	1745	3310	107-109
PhCO-ala-OEt	1650	1720	3320	110-113
PhCO-phe-OEt	1625	1745	3350	95-97
PhCO-val-OEt	1635	1725	3360	80-81
PhCO-leu-OEt	1630	1740	3300	65-67
PhCO-Meth-OEt	1640	1750	3310	79-82
PhCO-gly-OEt	-	-	-	58-60 (measured) 60.5 (published)

Note : the yield of the above amino acid esters range was (70-80%).

Results and Discussion:

Amino acid hydrazides (N-acetyl tyrosyi to N-benzoyl methionyl hydrazide) were prepared by treatment of the corresponding esters with hydrazine hydrate as described in the experimental part. Their IR spectra (Table 2) shows the main absorption bands at 1620-1650 cm^{-1} for CONH 3110-3200 cm^{-1} for NH amide stretching absorption and 3300-3400 cm^{-1} for NH_2. The ^{1}HNMR spectra of the above hydrazides showed the following main resonating signals 3.2-3.6 ppm, 8.2-9.0 ppm for NH_2 and NH amide respectively.

The compounds {7-chloro-2 (N-Acetyl tyrosyl hydrazido) -4,5-4-dioxopyrano [3,4-e] -1, 3-oxazine-4,5-dione},4a to { 7-chloro-2- (N-benzoyl methionyl hydrazido) -4, 5-dioxopyrano [3, 4-e]-1, 3-oxazine-4,5-dione} 4i were prepared according to the well known procedure [28,29] . Their structures were verified using IR, NMR spectra (Table 3). The IR spectra shows the following main signals 1630-1640 cm^{-1} for CONH, 1660-1670 for other type amide linkage, 3280-3300 cm^{-1} for amine stretching absorption together with other oxazine C=N, C=O absorption bands. The NMR spectra shows main resonating signals at 6.3-6.5 ppm for pyronic proton, broad band for NH, NH_2 of the hydrazide moiety as illustrated in (Table 3) together with the other protons of the remainder hydrazide moiety . The above information suggests the replacement of the 2-benzyl thio group by the hydrazide groups, except for compound 2b in which the methyl thio group was retained giving similar unexpected result of our previous work [10] (compound 2a) in which the hydrazide adds to the C=N of the oxazine ring. The evidence came from the spectral data (Table 3) and the sodium fusion test which gives +ve sulfur test.

Table (2): IR, NMR spectral data for amino acid hydrazides

Amino acid hydrazide	m.p. °C	Yield %	IR cm^{-1}				^{1}HNMR □ppm
			C=O		NH	NH_2	DMSO-d_6
Acetyl tyrosyl	239-242	65	1620	1660	3050	3300	2.2 (d, 2H)CH_2, 2.4 (s, 3H) CH_3, 3.1 (t, 1H) CH, 3.9 (b, 2H) NH_2, 6.2-6.7 (Abq, 4H), Ar-H, 7.7, 8.4 (b, 2H) 2NH, 8.7 (b, H) OH.
Acetyl cysteinyl	135-137	65	1650	1670	3150	3400	1.3 (t, 1H) SH, 2.0 (b, 2H) CH_2, 2.0 (b, CH_2, CH, CH_3), 4.2 (b, 2H)NH_2, 7.9, 8.2 (b, 2H), 2NH.
Benzoyl tyrosyl	249-251	70	1625	1660	3100	3300	2.4 (d, 2H) CH_2, 2.8 (t, 1H) CH, 4.1 (b, 2H) NH_2, 6.6-7.6 (m, 9H) Ar-H, 8.1, 8.3 (b, 2H) 2NH, 9.0 (b, 1H) OH
Benzoyl alamyl	100-102	72	1630	1660	3150	3300	1.2 (d, 3H) CH_3, 2.3 (q, 1H) CH, 3.1 (b, 2H) NH_2, 6.2-6.5 (m, 5H), Ar-H, 8.3, 8.6 (b, 2H) 2NH
Benzoyl phenyl ananyl	194-196	74	1640	1675	3150	3400	2.6 (d, 2H) CH_2, 2.8 (t, 1H) CH, 3.7 (b, 2H) NH_2, 6.6-7.3 (b, 10H), Ar-H, 7.9, 8.6 (b, 2H) 2NH
Benzoyl glycyl	154-156	70	1650	1655	3250	3400	1.8 (d, 2H) CH_2, 3.6 (b, 2H) NH_2, 7.3-7.7 (m, 5H), Ar-H, 8.2-8.5 (b, 2H) 2NH
Benzoyl valyl	209-211	78	1620	1650	3200	3300	0.7 (d, 6H) $2CH_3$, 1.0 (m, 1H) CH, 3 (t, 1H) CH, 3.2 (b, 2H) NH_2, 7.3 (m, 5H), Ar-H, 8.8, 9 (b, 2H) 2NH
Benzoyl leucyl	152-153	75	1625	1645	3150	3300	0.7 (d, 6H) $3CH_2$, 1.35 (m, 1H) CH, 1.9 (t, 2H) CH_2, 2.8 (t, 1H) CH, 3.2 (b, 2H) NH_2, 6.8-7.7 (m, 5H), Ar-H, 8.8, 9.2 (b, 2H) 2NH
Benzoyl methionyl	164-165	72	1630	1660	3110	3350	1.7 (s, 3H) CH_3, 2.5 (m, 2H) CH_2, 2.7 (t, 2H) CH_2, 3.0 (m, 1H) CH, 3.3 (b, 2H) NH_2, 6.8-7.4 (m, 5H), Ar-H, 8.4. 8.6 (b, 2H) 2NH

Table (3): IR, NMR spectral data for compounds 2b, 3 and (4a-i)

Comp. No.	m.p. °C	Yield %	IR cm^{-1}						^{1}HNMR □ppm DMSO-d_6
			C=N	4C=O	5C=O	HN	C=O	NH	
2b	162-164	80	1600	1725	1740	1640	1660	3300	2.2 (s, 3H) CH_3, 2.6 (d, 2H) CH_2, 3.1 (b, 1H) CH, 5.2-5.5 (b, 2H) 2NH, 6.8 (s, 1H)=CH, 7.1-7.9 (m, 9H) Ar-H, 8.2-8.3 (b, 2H) 2NH, 7.8 (b, 1H) OH
3	77-79	70	1590	1725	1760	1640	1675	3300	0.9 (t, 3H) CH_3, 3.7 (m, 2H) CH_2, 4.4 (m, 1H) NH, 6.9 (s, 1H)=CH, 8.7-8.9 (m, 2H) 2NH
4a	149-151	70	1600	1730	1740	1640	1660	3350	1.9 (d, 2H) CH_3, 2.2 (s, 3H) CH_3, 2.7 (t, lH) CH, 3.9 (b, 1H) NH, 6.3 (s, 1H)=CH, 6.5-7.3 (m, 4H) Ar-H, 7.9-8.31 (m, 2H) 2NH, 8.8 (b, 1H) OH
4b	102-104	72	1590	1720	1745	1640	1670	3300	1.4 (t, 1H) SH, 1.7 (t, 2H) CH_2, 2.0 (b, 3H) CH_3, 3.7 (b, 1H) NH, 6.3 (s, 1H) =CH, 8.2, 8.8 (b, 2H) 2NH
4c	139-140	75	1590	1720	1760	1630	1675	3350	2.3 (b, 2H) CH_2, 2.8 (t, 1H) CH, 4.3 (b, 1H) NH, 6.5 (s, 1H) =CH, 6.9-7.8 (m, 9H) Ar-H, 7.9, 8.1 (b, 2H) 2NH, 8.5 (b, 1H) OH
4d	124-127	80	1690	1750	1760	1640	1660	3350	1.8 (d, 2H) CH_2, 2.3 (s, 3H) CH_3, 3.7 (b, 1H) NH, 6.3 (s, 1H) =CH, 6.8-8 (m, 5H) Ar-H, 8.3-8.6 (b, 2H) 2NH
4e	102-103	74	1590	1720	1760	1630	1660	3300	2.0 (d, 2H) CH_2, 2.3 (b, 1H) CH, 3.4 (b, 1H) NH, 6.3 (s, 1H) =CH, (6.5-7.5 (b, 10H) Ar-H, 7.7, 8.2 (m, 2H) 2NH
4f	157-159	75	1600	1720	1730	1640	1660	3300	2.7 (b, 2H) CH_2, 3.2 (b, 1H) NH, 6.2 (s, 1H) =CH, 6.5-7.1 (m, 5H) Ar-H, 7.9, 8.3 (m, 2H) 2NH
4g	199-201	70	1590	1720	1760	1640	1670	3380	1.3 (s, 6H) $2CH_3$, 2.3 (m, 1H) CH, 2.8 (b, 1H) CH, 4.4 (b, 1H) NH, 6.5 (s, 1H) =CH, 7.2-7.8 (m, 5H) Ar-H, 8.2-8.3 (b, 2H) 2NH
4h	118-121	75	1590	1720	1760	1630	1670	3350	1.2 (t, 6H) $2CH_3$, 2.0 (b, 1H) CH, 2.3 (t, 2H) CH_2, 2.8 (b, 1H) CH, 4.3 (b, 1H) NH, 6.5 (s, 1H) =CH, 7.2-7.8 (m, 5H) Ar-H, 8.4-8.8 (b, 2H) 2NH
4i	200-202	70	1590	1720	1730	1640	1660	3280	1.3 (b, 2H) CH_2, 1.8 (b) for CH_2S, 2.3 (m, 1H) CH, 3.5(b,1H)NH, 6.5 (s, 1H) =CH, 6.6-7.1 (m, 5H) Ar-H, 8.3-8.5 (b, 2H) 2NH

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