Synthesis and Study of Acetylenic Amines Derivatives Containing Sulfonamido, β-Naphthoxy and Hippurate Groups

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Abstract

New derivatives of acetylenic amines containing sulfonamido, β-naphthoxy and hippurate groups have been synthesized through Mannich reaction which involved reaction of N-(1,1-dimethylpropargyl) benzene sulfonamide, propargyl-β-naphthyl ether and propagyl hippurate with paraformaldehyde and secondary amines. The structures of the synthesized compounds have been elucidated by physical and spectroscopic methods. Some of the synthesized compounds showed biological activity as antibacterial agents.

الخلاصة

حضرت مشتقات جديدة لامينات استيلينية حاوية على مجـاميع الـسلفونباميدو والبيتـا-نفثوكـسي والهيبورات من خلال تفاعل مانخ الذي تضمن مفاعلة N-(1،1-ثنائي مثيل بروبرجيل) البنزين سـلفوناميد، وبروبرجيل-β-نفثيل ايثر، وبروبرجيل الهيبيورات مع الفورمالدهايد والامينات الثانوية، وتم اثبات الـصيغ التركيبية للمركبات المحضرة باستخدام الطرائق الفيزياوية والطيفية، وأظهر قسم من المركبـات المحـضرة فاعلية بايولوجية كعوامل مضادة للبكتريا.

Introduction

Most of the pharmaceutically active acetylenic amines have been synthesized by the Mannich reaction in which active hydrogen containing compounds react with formaldehyde and ammonia or primary or secondary amines to produce Mannich bases [1]. These compounds were characteristic by different pharmacological activities such as hypertensive agents [2], anticholinergic agents [3], antispasmodics [4], anticancer agents [5], oxotremorine antagonists [6] and antibacterial agents [7].

On the other hand, many of sulfonamides were found to be well known compounds named as sulfa drugs [8] for possessing biological activities as hypoglycemic [9], bactericidal [10], antineoplastic [11], anti-inflammatory [12] and antitubercular [13].

Moreover, the β-naphthol derivatives showed different biological activities such as anti-trysin, anti-plasmin, anti-kallikren, anti-thrombin and anticompliment activities [14] and anti-inflammatory activity [15].

In addition, hippuric acid was used in the synthesis of azlactones or 5-oxazolones which are intermidiate compounds of high importance in the syntheses of α-aminoacids and ketoacids [16], also hippuric acid takes part in the thyroxine synthesis cycle

for thyroxine is a hormone found as iodine derivative in the protien thyroglobulin which occurs in the thyroid gland [16].

This paper is concerned with the introduction of sulfonamido, β-naphthoxy and hippurate groups to study the biological activity in these synthesized acetylenic amines.

Experimental

Melting points were measured by Gallenkamp melting point apparatus and are uncorrected. I.R. spectra were recorded by Pye Unicam SP 2000 Infrared Spectrophotometer as KBr disc. U.V. spectra were obtained from Shimadzu U.V. Visible Recording Spectrophotometer U.V. 160. CHN microanalyses were achieved by Elemental Analyzer Carlo Erba Stramentazion Model 1106.

Methods of Preparation:

Three series of acetylenic amines derivatives have been synthesized by following different method of preparation as shown below:

I- Preparation of Sulfonamido Acetylenic Amines Dervatives (I_{a-f}):

1-Preparation of N-(1,1-Dimethyl propargyl) Benzene Sulfonamide (I_a):

Modified method for the reference method [17] was applied to prepare this new compound (I_a).

Benzene sulfonyl chloride (0.2 mole) was dissolved in dry pyridine (40 ml), then 1,1-dimethyl propargyl amine (0.2 mole) was added drop by drop with stirring for 10 mint. The temperature was raised to about 70°C. After cooling of the mixture, excess of water was added with stirring so that the oily product was changed to solid precipitate. The precipitate was filtered, washed with cold water, dried and recrystallized from benzene-pet. ether (80-100°C) to obtain the desired product (I_a) as a white crystals as shown in Tables (1,2).

2-Preparation of N-(4-Amino-1,1-Dimethyl-2-Butynyl) Benzene Sulfonamides (I_{b-f}):

General Method (Mannich Reaction)[18]

Acetylenic compounds (0.03 mole) was mixed with the secondary amine (0.036 mole) in a round bottom flask fitted with a reflux condenser. The mixture was cooled to 0°C in ice bath and paraformaldehyde (0.036 mole) and CuCl (0.06 gm) in peroxide-free dioxane (16 ml) were added. The reaction mixture was cooled again to 0°C, and glacial acetic acid (4.5 ml) was added dropwise with shaking. The mixture was stirred at room temperature for 5 minutes, then at 90°C for 2 hrs.

After cooling, water (100 ml) was added and the reaction mixture was acidified to (pH=1) by dropwise addition of 1:1 (HCl: H_2O) with stirring, then extracted with (2×50 ml) of ether. The aqueous phase was made alkaline with saturated solution of sodium bicarbonate. The precipitate was filtered, washed several times with water, then dried and recrystallized from benzene-pet. spirit (80-100°C) to obtain the desired products (I_{b-f}) as shown in Tables (1,2).

3-Preparation of Benzene Sulfonamide Sodium Salt [19]:

Benzene sulfonamide (0.1 mole) was dissolved in sodium hydroxide solution (0.1 mole) in water (10 ml). The solution was filtered and evaporated to dryness to obtain a white powder of sodium salt.

4-Preparation of N-Propargyl Benzene Sulfonamide (Ii):

This new compound was prepared according to new preparation method as shown below:

Benzene sulfonamide sodium salt (0.1 mole) was added to a solution

of propargyl bromide (0.1 mole) in dimethyl sulfoxide (15 ml). The mixture was heated on a water bath at (50-60°C) for 90 mint with stirring. After cooling, cold water (30 ml) was added with stirring till the oily product turned to solid precipitate. The precipitate was filtered, washed with cold water and dried, then recrystallized from benzene to obtain the desired product as a white needle crystals of 45% yield and m.p. (77-79°C).

The CHN miroanalysis, found (calc.) was C, 54.88 (55.38); H, 4.39 (4.61); N, 7.08 (7.17).

υ_{N-H} 3310 cm^{-1}

$\upsilon_{C\equiv C}$ 2060 cm^{-1}

$\upsilon_{\equiv C-H}$ 3220 cm^{-1}

$\upsilon_{S=O}$ 1370 &1225 cm^{-1} (assym.& sym.)

λ_{max} ($CHCl_3$) 262 nm

On using N-propargyl benzene sulfonamide (Ii) in Mannich reaction with paraformaldehyde and different secondary amines, the products were gumy and all the attempts to purify and recrystallize these products were unseccessful so remained unidentified.

II- Preparation of β-Naphthoxy Acetylenic Amines derivatives (II_{a-i}):

1-Preparation of Sodium-β-Naphthoxide [20]:

β-Naphthol (0.015 mole) was dissolved in a solution of sodium hydroxide (0.015 mole) in water (15 ml). The solution was evaporated to dryness to obtain a coffee powder of sodium-β-naphthoxide.

2-Preparation of Propargyl-β-naphthyl Ether (II_a):

This new compound (II_a) was prepared according to new preparation method as shown below:

Propargyl bromide (0.012 mole) was added to a solution of sodium-β-naphthoxide (0.012 mole) in dimethyl sulfoxide (15 ml). The mixture was heated on a water bath at (50-60°C) for 1 hr with stirring. After cooling, cold water (50 ml) was added with stirring till the oily product turned to solid precipitate. The precipitate was filtered, washed with cold water and recrystallized from ethanol-water to obtain a brown color crystals of compound (II_a) as shown in Tables (3, 4).

3-Preparation of 4-Amino-2-Butynyl-β-naphthyl Ethers (II_{b-i}):

These compounds (II_{b-i}) have been prepared according to the Mannich reaction as described in method (I-2), and the recrystallization process was carried out from ethanol-water to obtain the desired products (II_{b-i}) as shown in Tables (3,4).

III-Preparation of Hippurate Acetylenic Amines Derivatives (III_{a-i}):

1. Preparation of Sodium Hippurate:

Hippuric acid (0.02 mole) was dissolved in a solution of sodium bicarbonate (0.02 mole) in water (15 ml). The solution was evaporated to dryness to obtain a white powder of sodium hippurate.

2. Preparation of Propargyl Hippurate (III_a):

This new compound (III_a) was prepared according to new preparation method as shown below:

Propargyl bromide (0.02 mole) was added to a solution of sodium hippurate (0.02 mole) in dimethyl sulfoxide (15 ml). The mixture was heated on a water bath at (70-80°C) for 90 mint. with stirring. After cooling, cold water (30 ml) was added with stirring till the oily product was changed to solid precipitate. The precipitate was filtered, washed with cold water and dried, then recrystallized from benzene to obtain a white crystals of compound (III_a) as shown in Tables (5, 6).

3. Preparation of 4-Amino-2-Butynyl Hippurate Derivatives (III_{b-i}):

These compounds (III_{b-i}) have been prepared according to the Mannich reaction as described in method (I-2), and the recrystallization process was carried out from benzene-pet. spirit (80-100°C) to obtain the desired products (III_{b-i}) as shown in Tables (5,6).

Results and Discussion

It is well known that many acetylenic amines derivatives are pharmaceutical active compounds. This fact was indicated from the previous studies [2-7]. Accordingly, the introduction of groups such as sulfonamido, β-naphthoxy and hippurate in the skeleton structure of the acetylenic amines may lead to improve biological activity of these compounds.

Therefore, three series of acetylenic amines derivatives have been synthesized from different methods. These methods involved formation of N-(1,1-dimethylpropargyl) benzene sulfonamide (I_a), including N-propargyl benzene sulfonamide (I_g), propargyl-N-naphthyl ether (II_a), and propargyl hippurate (III_a). These propargyl compounds were allowed to be reacted through Mannich reaction with paraformaldehyde and secondary amines to produce Mannich products as shown in Schemes (1), (2) and (3).

The synthesized acetylenic amines derivatives have been investigated according to their physical and spectroscopic data (I.R., U.V.) [21] and CHN microanalysis. Other supporting evidences is the positive Tollen test for acetylenic hydrogen which became negative test in Mannich products, also the positive picrate formation test for the tertary amino group in the synthesized acetylenic amines compounds.

I.R. spectra of compounds (I_{a-f}) as indicated in Table (2) showed two absorption bands for assymmetric and symmetric ($\upsilon_{S=O}$) at (1350-1380) cm^{-1} and (1100-1130) cm^{-1} respectively, weak band for $\upsilon_{C\equiv C}$ at (2050-2080) cm^{-1}, broad band for υ_{N-H} at (3300-3340) cm^{-1} and the $\upsilon_{\equiv C-H}$ in compound (I_a) at 3210 cm^{-1} had disappeared in Mannich products.

U.V. spectra of compounds (I_{b-f}) showed bathochromic shift in λ_{max} (261-263 nm) as compared with compound I_a (λ_{max} 256 nm) due to the conjugation effect on the electronic transition ($n \longrightarrow \pi^*$) as shown in Table(2).

I.R. spectra of compounds (II_{a-i}) showed strong absorption band for υ_{C-O-Ar} at (1230-1270) cm^{-1}, three absorption bands for the skeleton vibrations of aromatic ring at (1490-1610) cm^{-1}, weak band for $\upsilon_{C\equiv C}$ at (2050-2080) cm^{-1} and the $\upsilon_{\equiv C-H}$ in compound (II_a) at 3230 cm^{-1} had disappeared in the spectra of Mannich products as shown in Table (4).

U.V. spectra of compounds (II_{b-i}) showed bathochromic shift in λ_{max} (261-266 nm) as compound with compound II_a (λ_{max} 258 nm) due to the conjugation effect on the electronic transition ($n \longrightarrow \pi^*$) as shown in Table (4).

I.R. spectra of compounds (III_{a-i}) showed two strong absorption bands for amidic $\upsilon_{C=O}$ and esteric $\upsilon_{C=O}$ at (1645-1675) cm^{-1} and (1740-1755) cm^{-1} respectively, weak band for $\upsilon_{C\equiv C}$ at (2140-2150) cm^{-1}, broad band for υ_{N-H} at (3330-3360) cm^{-1} and the $\upsilon_{\equiv C-H}$ in compound (III_a) at 3230cm^{-1} was disappeared in Mannich products as shown in Table (6).

In U.V. spectra of compounds (III_{a-i}), The bathochromic shift in λ_{max} (249-260) nm as compared with compound III_a (λ_{max} 231 nm) is due to the conjugation effect on the electronic

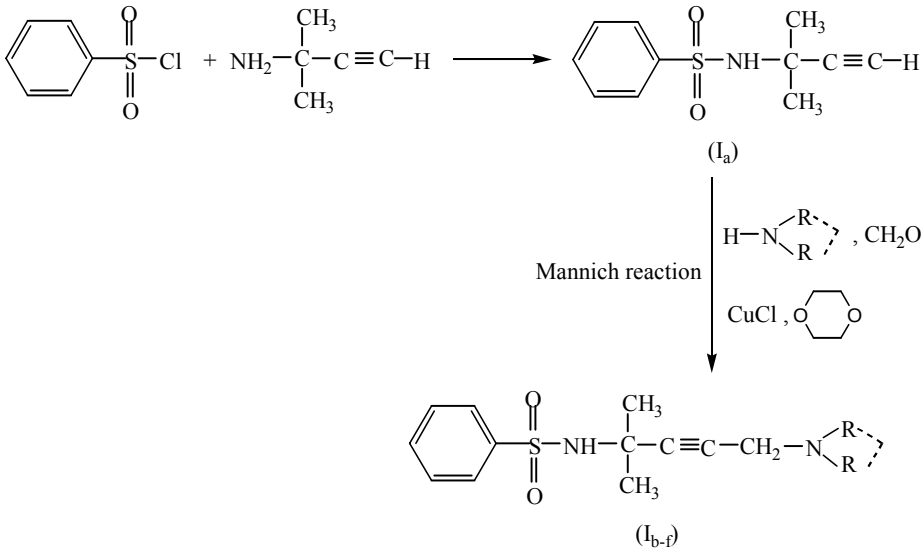
transition ($n \longrightarrow \pi^*$) as shown in Table (6).

The Biological Activity:

As shown in the introduction, many acetylenic amines derivatives were found to be biologically active compounds. Thus the new synthesized acetylenic amines derivatives were expected to be so. The study of biological activity was applied on the growth of two kinds of gram positive and gram negative bacteria by using disc diffusion method [23, 24]. This method was depended on the retardation activity test.

Staphelococcus aureus and Escherichia coli were used to represent the positive and negative bacteria of gram formula respectively.

The biological activity study was achieved on some of the synthesized acetylenic amines and the results indicated that some of the tested acetylenic amines especially hippurate acetylenic amines ($III_{c,f}$) showed high retraduction activity, others showed medium retardation activity against the tested bacteria as compared with that caused by standard antibiotics (Ampiclox and tetracycline) as illustrated in Table (7).



(I_a)

(I_{b-f})

Scheme (1)

Table (1): The physical properties of compounds (I_{a-f})

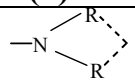
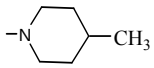
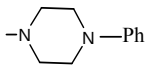
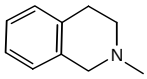
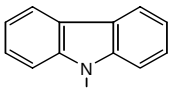
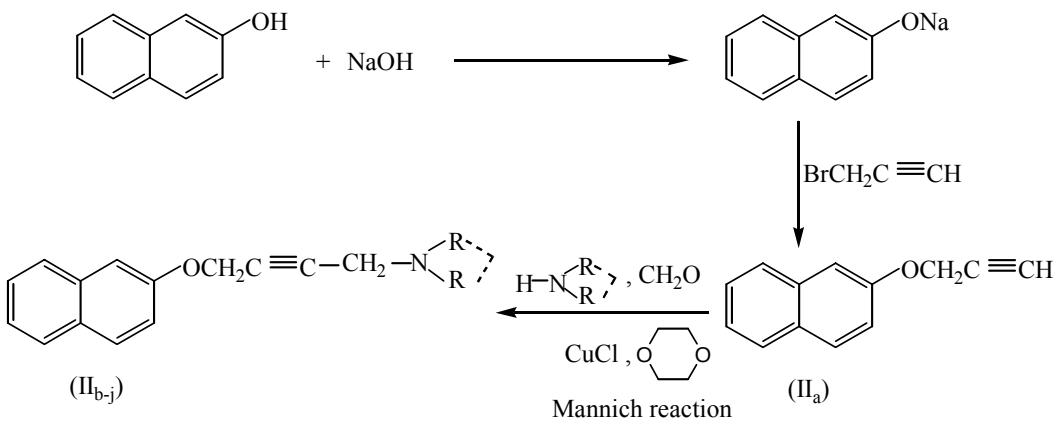
Compd. No.		% Yield	m.p. °C	CHN Found / calc.		
				%C	%H	%N
I_a	----	68	76-78	58.88 59.19	5.65 5.80	6.11 6.27
I_b		50	86-88	64.55 64.67	7.61 7.78	8.22 8.38
I_c		78	110-112	59.22 59.62	6.70 6.83	8.60 8.69
I_d		39	102-104	66.40 66.49	6.51 6.80	10.32 10.57
I_e		20	121-123	68.23 68.47	6.43 6.52	7.44 7.60
I_f		33	220-222	70.39 71.04	5.11 5.47	6.77 6.96

Table (2): Spectroscopic data of compounds (I_{a-f})

Compd. No.	I.R. cm^{-1} (KBr)					U.V. ($CHCl_3$)
	$\upsilon_{S=O}$ (s)	$\upsilon^*_{S=O}$ (s)	$\upsilon_{C\equiv C}$ (br)	$\upsilon_{\equiv C-H}$ (br)	υ_{N-H} (br)	λ_{max} (nm)
I_a	1120	1375	2050	3210	3300	256
I_b	1100	1370	2060		3325	266
I_c	1100	1375	2050		3300	261
I_d	1125	1380	2060		3300	261
I_e	1120	1360	2060		3330	264
I_f	1130	1350	2050		3340	263



Scheme (2)

Table (3): The physical properties of compounds (II_{a-i})

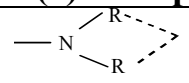
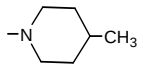
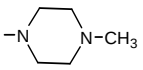
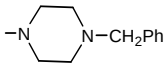
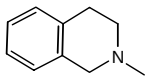
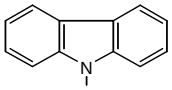
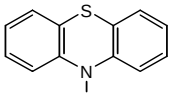
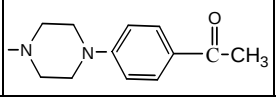
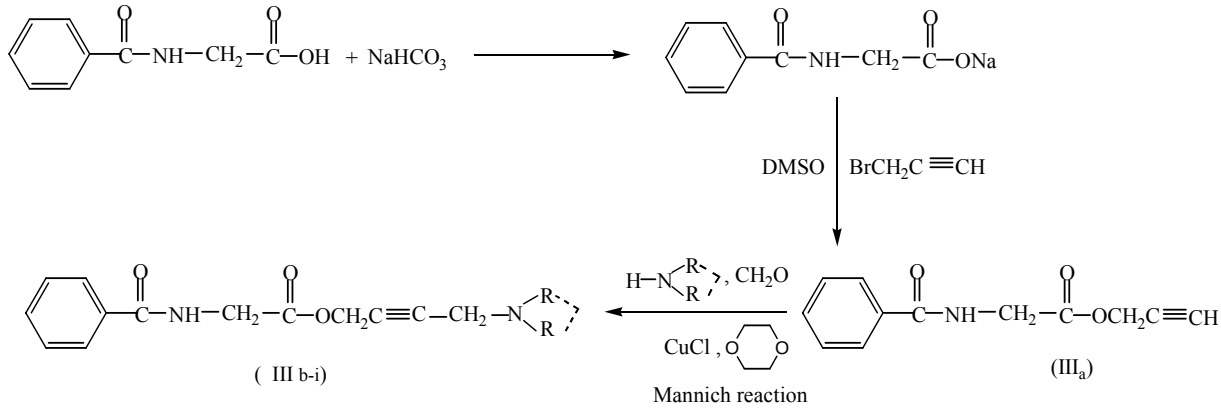
Compd. No.		% Yield	m.p. °C	CHN Found / calc.		
				%C	%H	%N
II_a	----	82	60 –62	85.49 85.71	5.34 5.49	-
II_b		50	76-78	81.39 81.91	7.81 7.84	4.60 4.77
II_c		32	68-70	76.55 76.86	6.55 6.76	4.78 4.98
II_d		55	159-161	76.89 77.55	7.36 7.48	9.23 9.52
II_e		68	146-148	80.44 81.08	7.01 7.02	7.32 7.56
II_f		76	214-216	83.89 84.40	6.31 6.42	4.11 4.28
II_g		50	298-301	85.79 86.42	5.10 5.26	3.66 3.87
II_h		70	136-138	78.79 79.38	4.66 4.83	3.50 3.56
II_i		40	140-142	78.13 78.39-	6.49 6.53	6.93 7.03

Table (4): Spectroscopic data of compounds (II_{a-i})

Compd. No.	I.R. cm^{-1} (KBr)				U.V. ($CHCl_3$) λ_{max} (nm)
	υ_{Ar-O-C} (s)	$\upsilon_{C \ldots C}$ (s)	$\upsilon_{C\equiv C}$ (br)	$\upsilon_{\equiv C-H}$ (s)	
II_a	1240	1600, 1580, 1510	2060	3230	258
II_b	1270	1610, 1580, 1500	2050		262
II_c	1240	1600, 1575, 1510	2060		264
II_d	1270	1610, 1580, 1490	2050		261
II_e	1250	1610, 1580, 1500	2080		261
II_f	1270	1600, 1575, 1510	2050		261
II_g	1230	1610, 1580, 1500	2060		262
II_h	1270	1600, 1580, 1500	2050		263
II_i	1230	1600, 1500	2060		266

Note: compound II_i showed $\upsilon_{C=O}$ (ketone) at 1665 cm^{-1}



Scheme (3)

Table (5): The physical properties of compounds (III_{a-i})

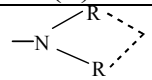
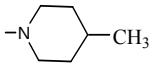
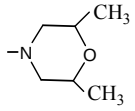
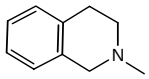
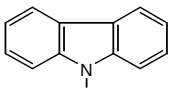
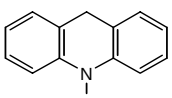
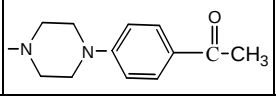
Compd. No.		% Yield	m.p. °C	CHN Found / calc.		
				%C	%H	%N
III_a	----	50	99-101	65.98 66.35	4.99 5.06	6.38 6.45
III_b		35	72-74	68.22 68.78	6.95 7.00	8.65 8.91
III_c		35	125-127	68.96 69.51	7.24 7.31	8.33 8.53
III_d		40	86-88	63.96 64.55	6.20 6.32	8.66 8.86
III_e		40	104-106	66.15 66.27	6.55 6.97	8.09 8.13
III_f		50	111-113	71.43 72.92	6.01 6.07	7.52 7.73
III_g		25	285-287	75.41 75.75	4.96 5.05	6.99 7.07
III_h		23	156-158	69.95 70.09	4.54 4.64	6.50 6.54
III_i		35	121-123	69.12 69.28	6.18 6.20	9.54 9.69

Table (6): Spectroscopic data of compounds (III_{a-i})

Compd. No.	I.R. cm^{-1} (KBr)					U.V. ($CHCl_3$) λ_{max} (nm)
	$\upsilon_{C=O}$ amide (s)	$\upsilon_{C=O}$ ester (s)	$\upsilon_{C\equiv C}$ (br)	$\upsilon_{\equiv C-H}$ (s)	υ_{N-H} (br)	
III_a	1675	1725	3130	3230	3370(s)	231
III_b	1650	1740	2120		3350	255
III_c	1645	1750	2140		3340	250
III_d	1660	1754	2120		3330	249
III_e	1650	1750	2120		3350	250
III_f	1640	1755	2140		3350	254
III_g	1660	1750	2150		3360	260
III_h	1660	1740	2130		3350	260
III_i	1670	1735	2140		3350	252

Note: Compound III_i showed another $\upsilon_{C=O}$ (ketone) at 1670 cm^{-1}

Table (7): The biological activity of some synthesized acetylenic amines

Compd. No.	Test Organism	
	E. coli	Sta. aureus
I_b	R	R
I_e	R	MS
I_f	R	R
II_f	R	MS
II_h	Ms	R
III_c	Ms	MS
III_f	S	S
Control		
Ampiclox	S	S
Tetracycline	S	MS

S= sensitive, MS = moderate sensitive
R = resistant

Note: biological activity test was achieved at Biological Dept. College of Science, University of Mosul

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