Synthesis of New Mannich Bases from Indole Derivatives

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Abstract:

This work includes two steps of synthesis, the first one is the synthesis of indole which was prepared according to literature of the reaction of phenyl hydrazine with acetaldehyde in glacial acetic acid afforded phenyl hydrazone of acetaldehyde , this product was fused with zinc chloride to give the indole.Reaction of cyclohexanone with phenyl hydrazine using the same procedure for the preparing giving 1,2,3,4-Tetrahydrocarbazole.

Second step involved synthesis of a series of (17) of mannich bases derivatives of indole and 1,2,3,4-Tetrahydrocarbazle. Mannich reaction involves the condensation of aldehyde usually formaldehyde with different secondary amine and with compound containing an activated hydrogen.The reaction illustrated by the following equation :

R2NH+HCHO+R\H→R2N-CH2-R+H2O

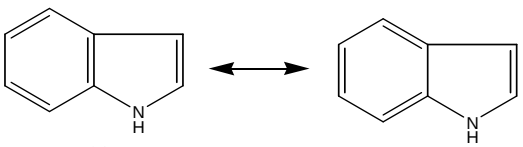
These compounds were characterized by U.V , FT-IR and ^{1}H-NMR spectra for two compounds.

The secondary amines that used to prepare mannich bases are:
N-methyl –N-phenyl amine, N,N-dimethyl amine, N,N- diphenyl amine, N-ethyl –N-phenyl amine, N,N-di-n-propyl amine, pyrrolidine, morpholine, N- methyl pipyridine, N,N-dibenzyl amine, N,N-di –n-butyl amine and N,N-di ethyl amine.

Key words : Indole, Mannich bases, Reaction of indole, Mechanism of mannich base

Introduction:

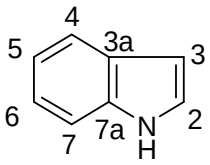
limited system, the two open carbons of the pyrrole ring as designated α- and β- , depending on the point of attachment of the substituent[3,4]. The most important reasonance structures for indole are (2) and (3) :



(2) (3)

The indole nucleus was found to be present in a varied group of products of natural occurrence in both the animal and the plant. Most of these products

Indole (1) (1-H- indole) was a benzopyrrole in which the benzene and pyrrole rings are united through the 2,3 – positions of the pyrrole[1,2].



The atoms are numbered consecutively, begining with nirogen, counter clockwise around the two fused rings with the bridge head carbons being denoted by 3a and 7a (1). According to the order and more

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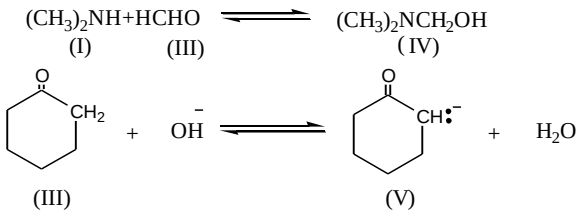
This compound was first encountered as a result of it's isolation from the seeds of *Abrus Precatorius* linn[9,10].

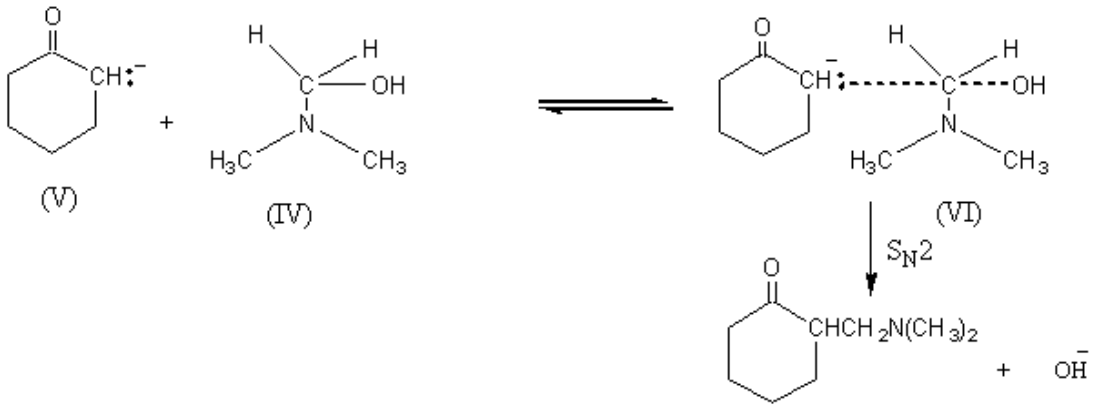
Mannich bases:

Mannich bases are very reactive, in fact they can easily transformed into numerous other compounds. Mannich bases have been investigated as potential biological agents, such as dyes for synthetic fibers, as reactive dyes and also as surface active compounds[11-14].

Libermann and Wanger[15] presented an attractive mechanism involving the formation of carbonium ion , $R_2NCH_2^+$ from the amine and formaldehyde and also the formation of a carbanion $R^{\ddots}$ by the removal of a proton from active hydrogen compound. The final , essentially irreversible step was the combination of carbonium ion and carbanion to yield the mannich base.

The mechanism in basic medium follows :

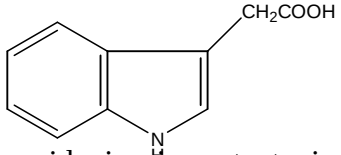




show marked physiological activity, and some are extremely complex in structure.

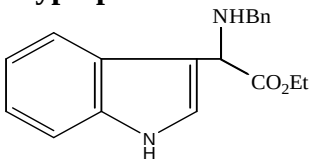
Natural products containing the Indole nucleus

1. Heteroauxin (indole 3- acetic acid)



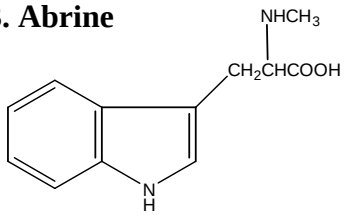
This acid is important in plant physiology because of the part it plays as a promoter of the growth of seedlings[5,6,7].

2. Tryptophan



Tryptophan derivatives are abundantly found in variety of naturally found compound that exhibit various physiological properties [8].

3. Abrine



heated under reflux in water bath for 3-17hr, and stirred at room temperature for 24hr. 5% NaOH was added to the reaction mixture, amorphous precipitate was formed and recrystallized from suitable solvent.

B. Preparation method was used as in A until basified with 5% NaOH solution. An oily layer was obtained, extracted with chloroform (2×10 ml). The extracts was evaporated to give dark oil.

Tables (IV) lists physical properties and condition of reactions, FTIR and UV absorption data for compounds (3-19) ^{1}HNMR for compounds (5) and (12).

Result and discussion:

The aim of the present work is to synthesize mannich bases from indole and 1,2,3,4-Tetrahydrocarbazole. This work contains two steps : the first one involved preparation of indole and 1,2,3,4-Tetrahydrocarbazole via the reaction of phenyl hydrazine with acetaldehyde or cyclohexanone to obtain indole and1,2,3,4-Tetrahydrocarbazole respectively.

These compounds were characterized by U.V and FTIR spectra.

The second step involved the reaction of indole and1,2,3,4-Tetrahydrocarbazolel with formaldehyde and different secondary amines to obtain new mannich bases. These compounds were characterized by U.V, FTIR and ^{1}HNMR spectra.

FTIR spectra of the prepared indole and 1,2,3,4- Tetrahydrocarbazole showed absorption bands at υ(3400) Cm^{-1} due to υ(N-H), υ(3030-3050)Cm^{-1}due to υ (C-H aromatic), υ (2890-2920) Cm^{-1}due to υ (C-H aliphatic) and υ (1600-1605) Cm^{-1}due to υ(C═C) aromatic [17,18].

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Materials and Methods:

IR spectra were recorded on (SHIMADZU) FT-IR-8400s spectrophotometer. Solid samples were run in KBr disc, Liquid were run as smears.

UV spectra were recorded on UV-Visible Spectrophotometer (SHIMADZU) UV-160A were performed by Baghdad University ,College of Science, Chemistry Department.

Melting point were determined in a (Gallen Kamp) m.p apparatus and are uncorrected.

^{1}H-NMR spectra were determined on jeol model JNM-LA 300 FT-NMR and JNM-LSH_3O solid and with Ultra Shield (Bruorgin) FT-NMR : 300 MHz in DMSO, $CDCL_3$ with tetramethyl silane as internal standard.

indole (1)[1]

This compound was prepared according to literature[1]:

Phenyl hydrazine (8ml) was added to a mixture of acetaldehyde (4.5ml) and glacial acetic acid (50ml). The solution boiled under reflux for 5min. The formed precipitate was purified by recrystallization from aqueous ethanol.

1,2,3,4-Tetrahydrocarbazole(2)[1]

This compound was prepared by the same procedure (1) used in the preparation of indole (1) except using of cyclohexanone (9ml) instead of acetaldehyde. The prepared compound was purified by recrystallization from aqueous ethanol.

Synthesis of Mannich Bases(3-19)

Mannich bases were prepared according to literature with some modifications [16]:

A. Formaldehyde (0.108 mol) was added to a mixture of indole or its derivatives (0.0042 mol) and 3ml acetic acid. The mixture was cooled to 5 °C, then secondary amine (0.0042 mol) was added to the mixture. The solution was

Table (III) lists UV absorption data for compounds(3-19).

^{1}HNMR spectrum for compound(5) (Fig 1)(Table IV)showed a signal at δ7-7.5 ppm was assigned to aromatic protons, a signal at δ3.3 ppm was assigned to H-proton of N-H group, a signal at δ2ppm was assigned to CH_2 protons, a signal at δ 8.2 ppm was assigned to H-proton of heterocyclic rings and a signal at 2.5ppm was assigned to DMSO.

^{1}HNMR spectrum for compound (12) (Fig 2) (Table IV)showed a signal at δ7-7.3 ppm was assigned to aromatic protons, a signal at δ5.2 ppm was assigned to H-proton of N-H group, a signal at δ3.1-3.3 ppm was assigned to protons of morpholine, a signal at δ 3.1 ppm was assigned to CH_2N and a signal at 1.7-1.9 was assigned to proton of cyclohexanone.

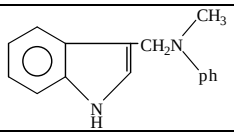
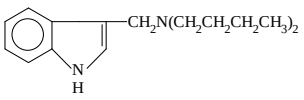
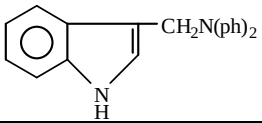
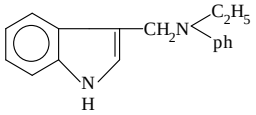
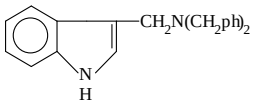
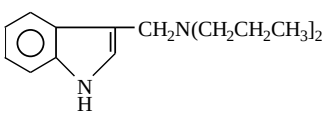
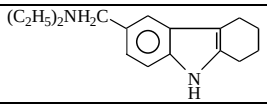
UV spectra of the prepared indole and 1,2,3,4-Tetrahydrocarbazole showed absorption peaks at λmax (258-372)nm due to π→ π* transition and absorption at λmax (517-920)nm due to n→ π* transition[17,18].

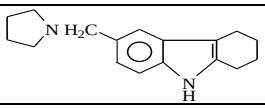
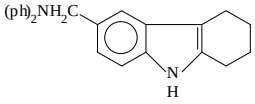
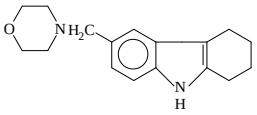
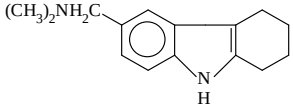
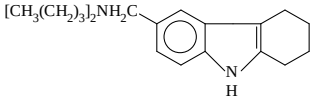
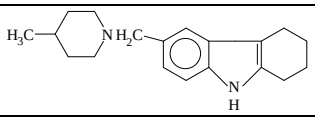
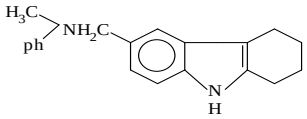
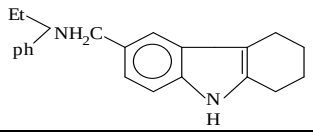
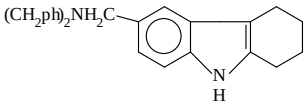
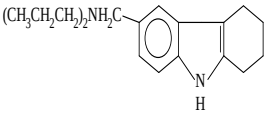
FTIR spectra of the prepared mannich bases(Fig 3-8) showed absorption bands at υ (3384-3450)Cm^{-1} due to υ (N-H), υ (3024-3100)Cm^{-1}due to υ (C-H aromatic), υ (2837-2950) Cm^{-1}due to υ (C-H aliphatic) and υ(1575-1639)Cm^{-1}due to υ(C=C) aromatic [17,18].

Table (II) lists FTIR spectral data for compounds(3-19).

UV spectra of the prepared mannich bases showed absorptions peaks at λmax (224-345)nm due to π→ π* and absorption peaks at λmax (517-972)nm due to n→ π* transition [17,18].

Table (1) Conditions of reactions and physical properties for Mannich bases (3-19)

Compd. No.	Scientific name	Chemical structure	Temp. of water bath °C	Heating time hr.	m.p °C	%Yield	Recrystallization solvent
3	3-((N-methyl-N-phenyl amino methyl))indole		65-70	17	oily	86	-----
4	3-((N,N-di-n-butylamino methyl)) indole		65-70	8	oily	77	-----
5	3-((N,N-diphenyl amino methyl))indole		55-60	4	178-180	86	DMSO
6	3-((N-ethyl-N-phenyl amino methyl)) indole		65-70	4	170-172 Dec.	84	Ethanol:Water 1 : 1
7	3-((N,N-dibenzylaminomethyl)) indole		55-60	4.5	128-129 Dec.	69	Ethanol :Acetone 1 : 1
8	3-((N,N-di-n-propylamino methyl)) indole		55-60	4	178-180 Dec.	77	Benzene
9	1,2,3,4-Tetrahydro-6-((N,N-diethylamino methyl)) carbazole		60-70	5	94-98	35	- Ethanol

10	1,2,3,4-Tetrahydro-6-((N-pyrrolidinomethyl)) carbazole		70-75	4	80-82	51	EtOH:H_2O 1 : 1
11	1,2,3,4-Tetrahydro-6-((N,Ndiphenylamino methyl)) carbazole		55-60	4.5	Oily	37	------
12	1,2,3,4-Tetrahydro-6-((N-morpholinomethyl)) carbazole		65-70	4	130-132	56	Benzene:ether 1 : 1
13	1,2,3,4-Tetrahydro-6-((N,Ndimethylamino methyl)) carbazole		60-70	3.5	125-127	71	EtOH:H_2O 1 : 1
14	1,2,3,4-Tetrahydro-6-((N,N-di-n-butyl aminomethyl)) carbazole		50-60	4	105-107	35	Ethanol:water 1 : 1
15	1,2,3,4-Tetrahydo-6-((4-methyl pipyridino methyl)) carbazole		55-60	4	90-92	60	Ethanol
16	1,2,3,4-Tetrahydro-6-((N-methyl-N-phenylamino methyl)) carbazole		65-70	4.5	155-157	50	Chloroform
17	1,2,3,4-Tetrahydro-6-((N-ethyl-N-phenylamino methyl)) carbazole		65-70	4	100-101	48	Ethyl acetate
18	1,2,3,4-Tetrahydro-6-((N,N-dibenzylamino methyl)) carbazole		55-60	4.5	oily	11	-----
19	1,2,3,4-Tetrahydro-6-((N,N-di-n-propylamino methyl)) carbazole		50-55	3.5	208-210 Dec.	51	Chloroform:ether 1 :1

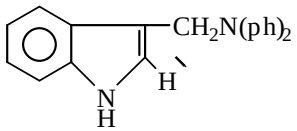
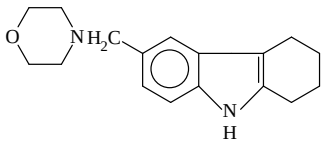
Table(2) FTIR spectral data for compounds(3-19)

Compd. No.	ν N-H cm^{-1}	ν C-H cm^{-1} Aromatic	ν C-H cm^{-1} Aliphatic	ν C=C cm^{-1} Aromatic	ν C-N cm^{-1}
3	**3409**	**3049**	**2900**	**1604**	**1456**
4	**3390**	**3100**	**2956**	**1639**	**1456**
5	**3394**	**3030**	**2980**	**1595**	**1463**
6	**3421**	**3024**	**2900**	**1630**	**1463**
7	**3384**	**3026**	**2950**	**1620**	**1450**
8	**3410**	**3049**	**2902**	**1577**	**1465**
9	**3411**	**3090**	**2925**	**1575**	**1465**
10	**3355**	**3030**	**2852**	**1600**	**1465**
11	**3350**	**3024**	**2927**	**1596**	**1465**
12	**3484**	**3026**	**2850**	**1590**	**1460**
13	**3384**	**3047**	**2837**	**1575**	**1461**
14	**3375**	**3026**	**2927**	**1616**	**1449**
15	**3350**	**3082**	**2925**	**1616**	**1465**
16	**3425**	**3095**	**2850**	**1610**	**1467**
17	**3450**	**3026**	**2836**	**1618**	**1463**
18	**3425**	**3060**	**2927**	**1590**	**1463**
19	**3448**	**3083**	**2850**	**1577**	**1463**

Table (3)UV absorption data for compounds (3-19)

Compound Number	λ max (nm)
3	345, 249
4	279,227
5	286,224
6	275,237
7	290,265
8	290,260
9	275,233
10	272,234
11	282,230
12	285,231
13	285,231
14	346,286,231
15	286-231
16	283,234
17	231
18	264
19	282,237

Table (4) ^{1}H-NMR data for compounds (5 and 12)

Compd. No.	Structure	δ H Amine ppm	δ H Aromatic ppm	δ N-H ppm	δ CH_2N ppm	δ other bands ppm
5		-	7-7.5 (m,14H)	3.3 (b, 1H)	2 (s, 2H)	8.2 (s, H) H^1
12		3.1-3.3 (m, 8H)	7-7.3(m, 3H)	5.2 (b, 1H)	3.1 (s, 2H)	1.7-1.9 (m, 8H) cyclohexane

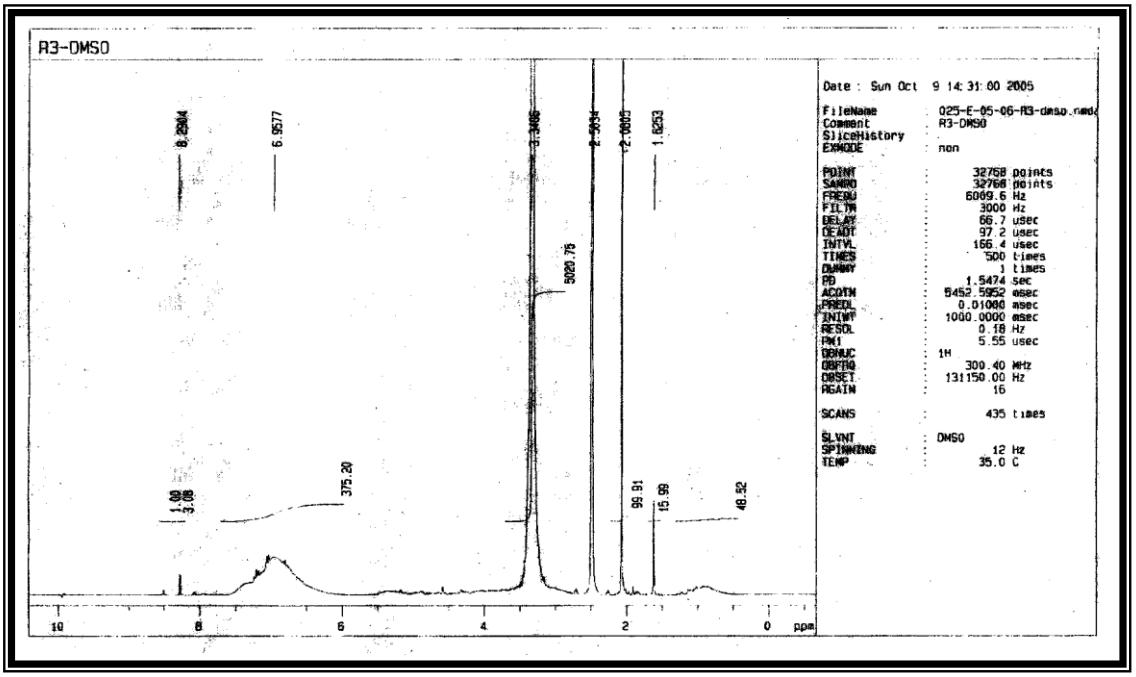
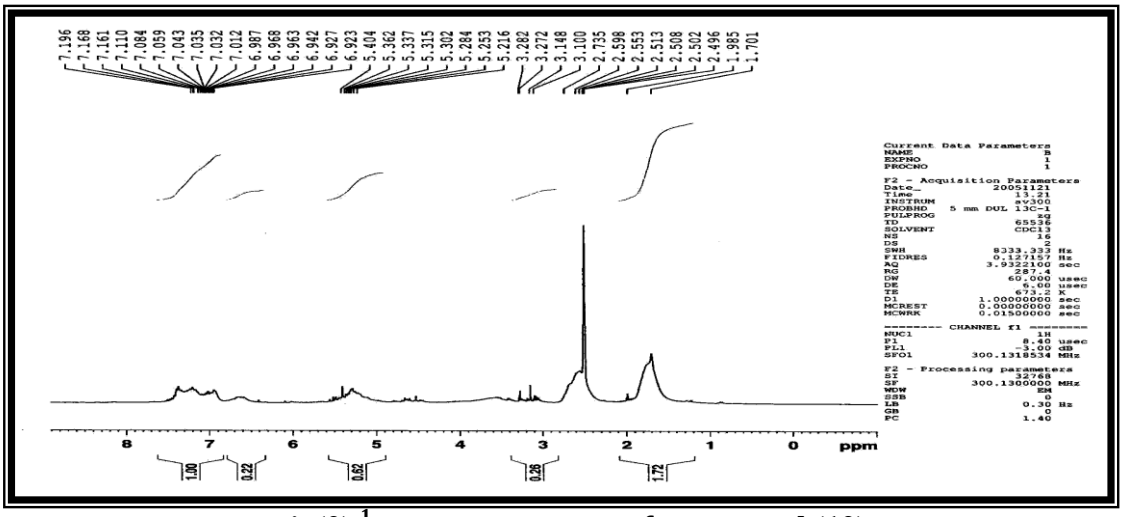


Fig. (1) : ^{1}H-NMR spectrum for compound [5]



Fig(2) ^{1}H-NMR spectrum of compound (12)

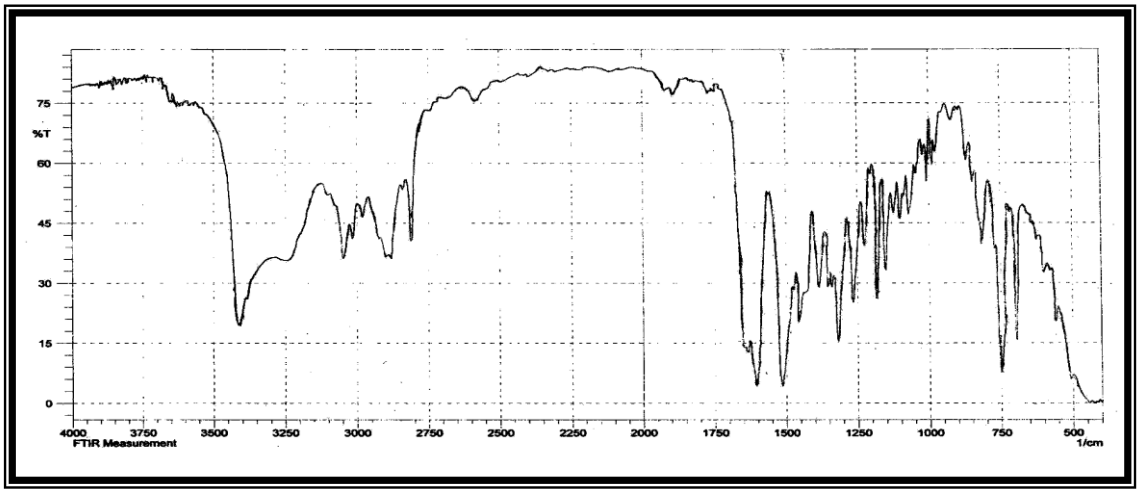


Fig. (3) : FT-IR spectrum for compound (3)

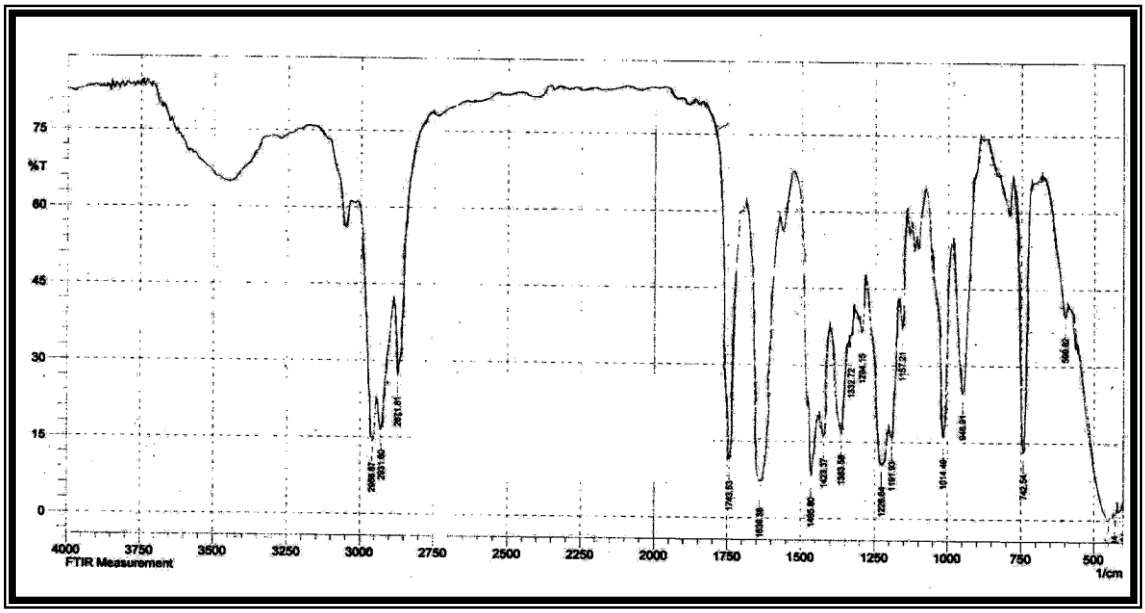


Fig. (4) : FT-IR spectrum for compound

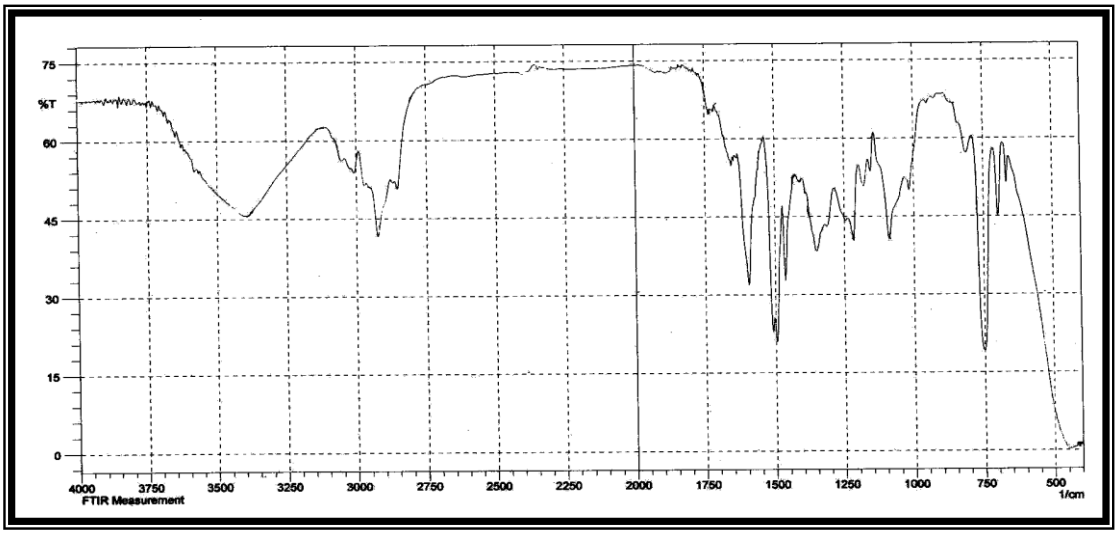


Fig. (5) : FT-IR spectrum for compound (5)

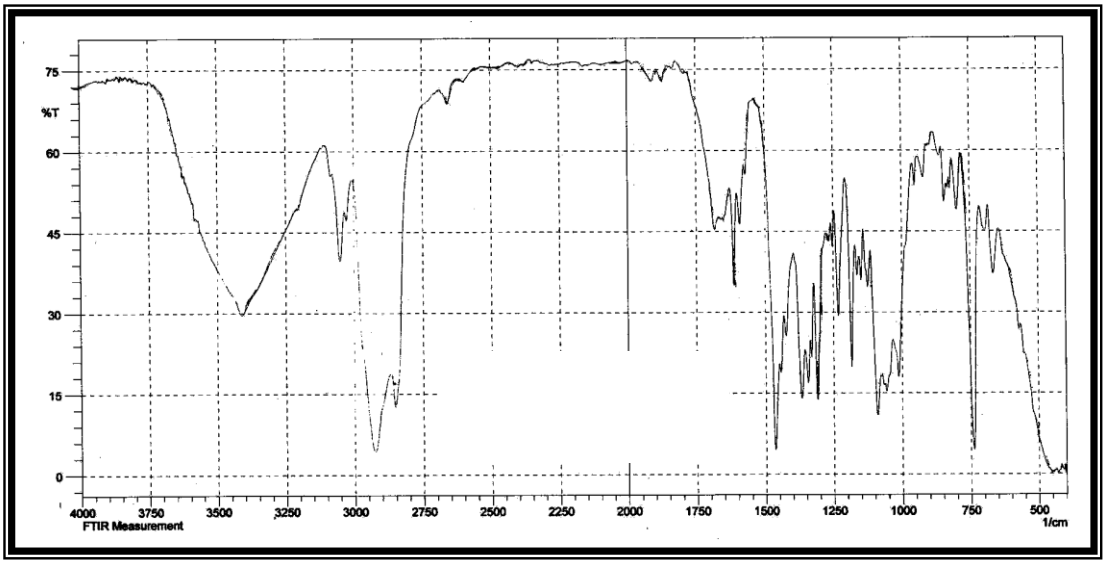


Fig. (6) : FT-IR spectrum for compound (9)

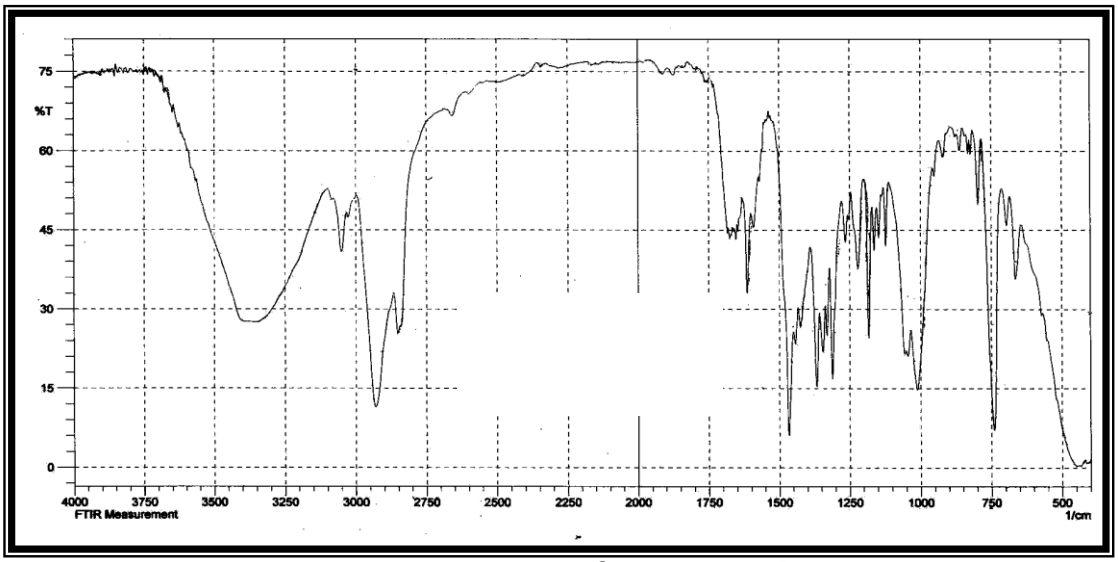


Fig. (7) : FT-IR spectrum for compound 10 (36)

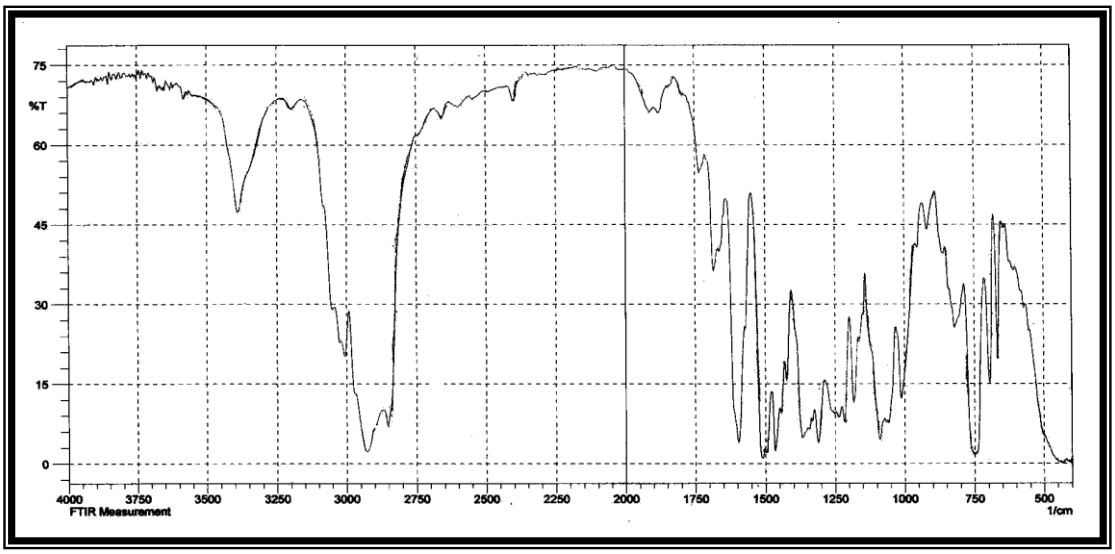


Fig. (8) : FT-IR spectrum for compound (11)

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تحضير قواعد مانخ جديدة من مشتقات الاندول

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الخلاصة:

يتضمن البحث خطوتين ، الخطوة الأولى هي تحضير الاندول من تفاعل فنيل هيدرازين مع الاستلديهايد بوجود حامض الخليك وناتج التفاعل هو الهيدرازون للاستلديهايد ثم صهر هذا الناتج مع كلوريد الزنك ليعطي الاندول.
أما المشتق الثاني فقد تم تحضيره من تفاعل السايكلوهكسانون مع فنيل هيدرازين باستعمال الطريقة نفسها المذكوره سابقا اعطت مركب 4،3،2،1- تتراهيدروكاربازول .
أما الخطوة الثانية فهي تحضير سلسلة من أملاح مانيخ مشتقة من الاندول و4،3،2،1- تتراهيدروكاربازول والتفاعل هو عبارة عن تكثيف الالديهايد (فورمالديهايد) ومشتق الاندول مع أمينات ثانوية مختلفة.
تم تشخيص هذه المركبات بالطرائق الطيفية باستخدام طيف الأشعة تحت الحمراء ، طيف الأشعة فوق البنفسجية وطيف الرنين النووي المغناطيسي لاثنين منها.