Synthesis and Characterization of Pharmacologically Important Acetylenic Amines Derived from Piperazine

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Abstract

Acetylenic amines are very important class of compounds for their pharmacological properties such as activity, low toxicity and easy to absorption from the body. More over these compounds are electron rich and easy to bond with receptor protein.

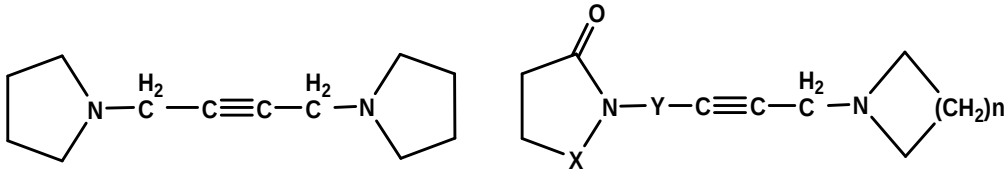
A number of pharmacologically important acetylenic amines derived from piperazine with expected activity as oxotremorine antagonist have been synthesized through Mannich reaction[1]. The compounds prepared by reaction of para aromatic substituting propynes with piprazine derivatives and formaldehyde in the presence of cuprous chloride as a catalyst. All the prepared compounds are characterized by elemental analysis and spectroscopic methods, the all physical and spectral data are showed in tables (1-3).

Key words: Acetylenic amines, Mannich reaction, Mannich bases, Piprazine

Introduction

Acetylenic amines constitute a class of chemical compounds that have received considerable attention due to the fact that a number of them are pharmacologically active compounds[2-4]. For example, a number of acetylenic amines are known to be pharmacologically important compounds[5-7]. Moreover, various prop-2-ynylamines are used as drugs or pesticides[8]. Some of the acetylenic amines that contain (CH_2–C≡C–CH_2-) function have been found to possess a high degree of specificity as central cholinergic or anticholinergic agents. Among these are tremorine[9] (1, 4-dipyrrolidino-2-butyne) (1) and a number of N-(dialkylamino-2-alkynyl) substituted succinimido[10,11] (2a) and pyrrolidones (2b)(Fig.1.).

The importance of the acetylenic bond in oxotremorine and antagonists of oxotremorine has been the subject of so much discussion. It has been suggested that the triple bond represents a region of high electron density which is capable of binding to the muscarinic receptors at the same site as the furan oxygen of muscarine and ester oxygen of acetylcholine[12]. It has also been claimed that the acetylenic bond is not considered essential for activity but favors entry in the central nervous system (CNS) by reducing the base strength[13].



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(2a) X = CH2 Y = CH_2, $(CH_2)_2$, $C(CH_3)_2$
(2b) X = O n = 2 - 4

Fig.1: Tremorine and N-(tert-aminoalkynyl) substituted succinimides and2-pyrrolidone

We report here with, the synthesis of a number of organic compounds that comprise both piperazine ring and acetylenic moiety.

Experimental

Preparation of Mannich bases (compounds1-12)[14,15].

These compounds where prepared through Mannich reaction between the acetylenic compounds (that is supplied from Aldrich and Fluka company but there are some researches that prepared acetylenic compounds as an intermediate from suitable starting aromatic derivatives and propargyl bromide with appropriate procedure), paraformaldehyde and piperazine derivatives as a secondary amine component as follows:

To a mixture of (0.01) mole of the propargylic derivatives and (0.01) mole of para formaldehyde in (50) ml peroxide – free dioxane was added (0.005) mole of the appropriate piperazine compound and a catalytic amount (0.12) g of cuprous chloride. The mixture was heated at 90^o C for (90) minutes. After cooling, the mixture was filtered and the filterate was poured into (100) ml of cold water. The solid compound was isolated and passed on a column of neutral alumina and eluted with chloroform. A pale yellow crystalline solid of Mannich bases (1-12) was obtained in each case.

The analytical data are recorded in table (1) and spectroscopic data (FT-IR analyzed in the North Oil Company in Kirkuk and the H^1-NMR, C^{13}-NMR, C.H.N analyzed in the Al- Albait University in Jordan) are collected in table (2) and (3).

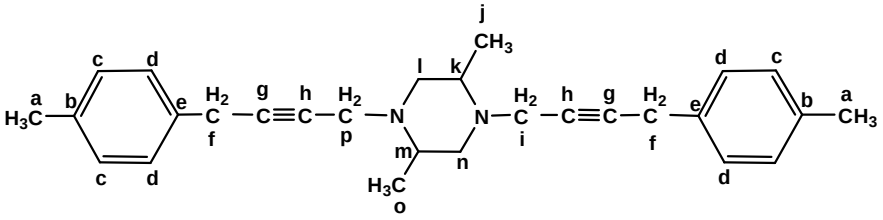
Table (1): Analytical data of Mannich bases (1-12)

Cpd. No.	% Yield	Color	M.P.	(C.H.N) / cal. (found)		
				% C	% H	% N
1	70	Yellow	146-148	84.28 (83.58)	8.16 (8.20)	7.56 (7.48)
2	63	Yellow	162-164	84.33 (83.90)	8.39 (8.45)	7.28 (7.20)
3	60	Pale yellow	154-156	84.37 (83.11)	8.60(8.72)	7.03 (7.00)
4	56	Yellow to brown	193-196	70.07 (70.12)	5.88 (5.81)	6.81 (6.77)
5	51	Brown	201-204	70.59 (70.63)	6.16 (6.09)	6.59 (6.49)
6	64	Brown	207-209	71.07 (71.18)	6.42 (6.41)	6.38 (6.31)
7	75	Pale yellow	178-179	66.65 (66.60)	5.59 (5.55)	12.96 (12.88)
8	86	Dark brown	182-185	67.25 (67.22)	5.87 (5.80)	12.55 (12.50)
9	73	Yellow	186-188	67.81 (67.79)	6.13 (6.01)	12.17 (12.00)
10	52	Yellow	198-189	77.38 (77.31)	7.58 (7.50)	15.04 (14.98)
11	60	Dark yellow	206-208	77.68 (77.65)	7.82 (7.81)	14.49 (14.41)
12	78	Dark yellow	214-216	77.96 (77.90)	8.05 (8.01)	13.99 (13.91)

Table (2): Spectroscopic data of Mannich bases (1-12) (IR, H^1-NMR)

Cpd. No.	*IR (cm^{-1})*						*NMR (δ, ppm)*						
	C-H(al.) str.(asy.,sy.)	C-H(ar.) str.	C-Cl str.	C-NO_2 str	N-H str.	N-H bend.	CH_3-ph	CH_3 piper. ring	CH_2 piper. ring	CH_3—N—	CH_2-ph	NH_2	aromatic
1	2981 2885	3180	-	-	-	-	2.31 (s,6H)	-	2.39 (s,8H)	3.15 (t,4H)	3.30 (t,4H)	-	6.90 (s,8H)
2	2960 2807	3030	-	-	-	-	2.36 (s,6H)	1.20 (d,3H)	2.3-2.6 (m,6H)	3.20 (t,4H)	3.34 (t,4H)	-	6.92 (s,8H)
3	2936 2860	3090	-	-	-	-	2.32 (s,6H)	1.15 (d,6H)	2.3-2.6 (m,4H)	3.12 (t,4H)	3.28 (t,4H)	-	6.98 (s,8H)
4	2921 2880	3179	660	-	-	-	-	-	2.40 (s,8H)	3.09 (t,4H)	3.31 (t,4H)	-	7.10,7.25 2 (d,4H)
5	2990 2798	3092	685	-	-	-	-	1.18 (d,3H)	2.3-2.6 (m,6H)	3.12 (p.r.t,4H)	3.28 (p.r.t,4H)	-	7.00,7.18 2 (d,4H)
6	2928 2845	3138	750	-	-	-	-	1.14 (d,6H)	2.3,2.6 (q,4H)	3.11 (p.r.t,4H)	3.30 (p.r.t,4H)	-	6.95,7.20 2 (d,4H)
7	2910 2870	3100	-	1350 1560	-	-	-	-	2.45 (s,8H)	3.11 (p.r.t,4H)	3.26 (p.r.t,4H)	-	7.25,8.10 2 (d,4H)
8	2912 2830	3180	-	1380 1610	-	-	-	1.23 (d,3H)	2.3-2.6 (m,6H)	3.12 (p.r.t,4H)	3.22 (p.r.t,4H)	-	7.28,8.00 2 (d,4H)
9	2920 2870	3074	-	1365 1580	-	-	-	1.18 (d,6H)	2.3,2.6 (q,2H)	3.13 (p.r.t,4H)	3.31 (p.r.t,4H)	-	7.28,8.11 2 (d,4H)
10	2934 2855	3153	-	-	3500	1289	-	-	2.40 (s,8H)	3.18 (t,4H)	3.27 (t,4H)	4.13 (s,4H)	6.30,6.91 2 (d,4H)
11	2960 2843	3069	-	-	3410	1294	-	1.16 (d,3H)	2.1-2.6 (m,6H)	3.16 (t,4H)	3.27 (t,4H)	4.08 (s,4H)	6.41,6.90 2 (d,4H)
12	2958 2878	3196	-	-	3360	1278	-	1.20 (d,6H)	2.2,2.5 (q,3H)	3.15 (q,4H)	3.26 (t,4H)	4.11 (s,4H)	6.35,6.90 2 (d,4H)

Table (3): C^{13} - NMR data of Mannich bases (1-12)

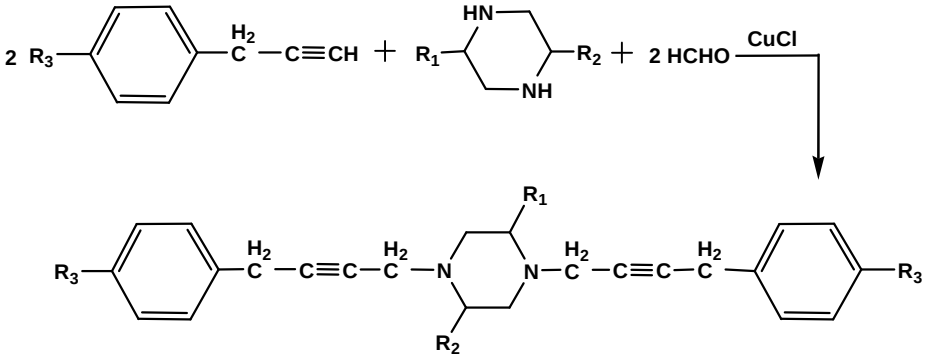


Cpd. No.	Carbon atoms symbol															
	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p
1	24.1	134.2	128.0	128.0	134.9	22.8	75.8	78.7	42.7	-	51.5	51.6	51.7	51.8	-	42.7
2	24.0	134.3	128.1	127.0	133.8	22.6	76.1	79.2	41.8	15.3	52.3	59.9	50.7	44.2	-	42.8
3	24.2	135.0	129.1	128.3	134.8	23.1	76.5	79.8	41.6	15.6	53.0	58.1	53.2	58.4	15.6	41.9
4	-	130.8	127.6	131.4	138.1	23.5	76.2	80.2	43.5	-	51.1	51.1	51.2	51.8	-	42.8
5	-	130.9	128.5	131.3	138.2	23.4	76.2	79.5	40.8	15.6	53.5	61.0	51.6	47.9	-	43.2
6	-	131.4	127.9	130.8	137.5	24.0	77.1	80.2	41.6	15.8	52.4	58.6	52.6	57.8	15.7	41.0
7	-	144.2	121.6	130.6	144.9	23.8	76.9	80.1	43.4	-	51.2	51.3	51.6	50.8	-	43.4
8	-	145.6	121.5	130.7	145.5	22.8	77.1	80.2	41.5	15.7	53.4	61.0	51.6	48.8	-	44.2
9	-	145.9	121.6	130.5	145.6	24.0	77.0	79.6	41.6	16.1	53.5	59.1	53.6	58.2	16.2	41.7
10	-	143.9	117.0	130.2	129.1	23.8	76.8	80.2	44.0	-	51.2	51.4	51.3	51.3	-	43.8
11	-	145.6	116.6	130.2	129.3	23.9	76.8	80.3	41.5	15.6	53.2	61.0	53.3	49.0	-	43.7
12	-	145.1	116.6	128.9	129.3	23.4	77.2	80.5	41.6	16.6	53.7	57.1	54.0	58.2	16.4	41.8

Results and Discussion

A number of compounds comprising both amino and ethynyl functions have been reported to possess a potential pharmacological value. For example N-(tert-aminoalkynyl) substituted succinimides and2-pyrrolidones (Fig.1) were reported to be potent in blocking the motor effects of the mascarinic agent oxotrcmorine[10,11,16].

As a variation of the above structures four series comprising twelve acetylenic amines (series I-IV) that are drug candidates with expected activity as oxotremoring antagonists have been synthesized through Mannich reaction using piperazine ring as the secondary amine component[17,18]. Those acetylenic compounds that are prepared in this work consist in their structure a phenyl (substituted) compounds, methyl (1-3), chloro (4-6), nitro (7-9) and amino (10-12) moieties.Thus the reaction between the piperazine (secondary amines) with propargylic derivatives in the presence of formaldehyde and catalytic amount of cuprous chloride produce compounds(1-12) that have not been reported in the literature previously. (Schemes 1).



Scheme (1)

Series I : N,N-Bis-[4-(p-tolyl) but-2-ynyl] piprazine derivatives

(1) $R_1 = R_2 = H$, $R_3 = CH_3$
(2) $R_1 = R_3 = CH_3$, $R_2 = H$
(3) $R_1 = R_2 = R_3 = CH_3$

Series II : N,N-Bis-[4-(4-chloro phenyl) but-2-ynyl] piprazine derivatives

(4) $R_1 = R_2 = H$, $R_3 = Cl$
(5) $R_1 = CH_3$, $R_2 = H$, $R_3 = Cl$
(6) $R_1 = R_2 = CH_3$, $R_3 = Cl$

Series III : N,N-Bis-[4-(4-nitro phenyl) but-2-ynyl] piprazine derivatives

(7) $R_1 = R_2 = H$, $R_3 = NO_2$
(8) $R_1 = CH_3$, $R_2 = H$, $R_3 = NO_2$
(9) $R_1 = R_2 = CH_3$, $R_3 = NO_2$

Series IV : N,N-Bis-[4-(4-amino phenyl) but-2-ynyl] piprazine derivatives

(10) $R_1 = R_2 = H$, $R_3 = NH_2$
(11) $R_1 = CH_3$, $R_2 = H$, $R_3 = NH_2$
(12) $R_1 = R_2 = CH_3$, $R_3 = NH_2$

These compounds were characterized by elemental analysis and spectroscopic means. The results of elemental analysis agree quite well with the assigned formulas for these compounds. Tables (1, 2 and 3) list the analytical and spectroscopic data of the acetylenic amines described in this work.

The infrared spectra clearly showed the absence of acetylenic absorption in all the compounds and this is not surprising in view of the highly symmetrical structure of the molecules so small or no change in dipole moment occurs during vibration.

In the H^1-NMR spectra, the two (CH_2) protons that are connected to the (C=C) function appeared as triplets (somewhat poorly resolved) due to long range coupling. However in compounds (2, 5, 8 and 11) where the piperazine ring carries (2-CH_3) groups, the diastereotopic (N-CH_2) protons are anisochronous due to the presence of methyl group in position (2) of the heterocyclic ring and thus appear as a triplet of quartet (tq) that is an AB part of the ABX_2 system due to coupling with (≡C-CH_2) protons across the triple bond.

For almost all organic molecules complete C^{13} spectra appear between low field carbonyl carbons and high methyl carbons in the range (0–200) ppm (δ) value. TMS is the common internal reference which is used for C^{13} - NMR (CMR). One of the important advantages of using (CMR) in organic chemistry is that many of the functional groups contains carbon atom are not contains hydrogen atom to study it in H^1-NMR and it directly observed in (CMR), another major advantages of C^{13} over H^1 magnetic resonance spectroscopy is the increased separation of chemically shifted signals about ten fold. The ensuing improvement in resolution is a powerful aid to structural analysis.

The state of hybridization is the dominating factors determining the chemical shift of carbon atom sp^3 hybrid carbon atom absorb up field while sp^2 carbon atoms absorb at lower field.

In aromatic compounds, the electro donating substitution (–NH_2,–Cl) delocalize their lone electron pairs into the (π) system, thus increasing the charge density at the ortho and para carbons. Substitutuents with lone pairs, thus, shield ortho and para carbons with the electro attracting groups have a deshielding influence [(19)].

The pharmacological importance of these compounds is to be tested later and needs further work.

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تحضير وتشخيص بعض الامينات الاسيتلينية المشتقة من الببرازين ذات فعالية بايولوجية متوقعة

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الخلاصة

تعتبر الامينات الاسيتلينية صنف مهم من المركبات بسبب صفاتها البايولوجية مثل الفعالية، سميته الواطئة وسهولة امتصاصها من قبل الجسم. وتكون هذه المركبات غنية بالالكترونات وبسهولة تكون آواصر مع البروتينات المستقبلة.

عدد من هذه الامينات الاسيتلينية ذات الفعالية البايولوجية المهمة والمشتقة من الببرازين ومع فعالية بايولوجية متوقعة كمضاد للاوكسوتريمورين قد حضرت من خلال تفاعل مانخ[1]. حيث حضرت هذه المركبات من تفاعل مشتقات البنزين الاسيتلينية المعوضة في الموقع بارا مع مشتقات الببرازين والفورمالديهايد بوجود كمية صغيرة من كلوريد النحاسوز كعامل مساعد. جميع هذه المركبات المحضرة قد شخصت بواسطة التحليل الدقيق للعناصر والطرق الطيفية. جميع القيم الفيزيائية والطيفية المقاسة موضحة في الجداول (1–3).