Novel Acetylenic Tricyclic Derivatives with Potential Monoaminooxidase Inhibitory Activity

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ABSTRACT

A new series of novel N- (4-tert-amino-2-butynyl) dibenzazepine were prepared and characterized by elemental analysis and spectroscopic techniques. Their effect on pentobarbitone sleeping-time in mice was investigated. All compounds showed an increase in the duration of hypnosis induced by pentobarbitone as reflected in prolongation of the sleeping-time relative to the control animals as a result of Monoaminooxidase inhibitory activity

Keywords: Tricyclic, Acetylenic, MAO inhibitors

INTRODUCTION

Tricyclic compounds such as amitriptyline, nortriptyline, imipramine and desipramine have been used in treating depression, anxiety and eating disorders, and sexual dysfunction (Spinks and Spinks, 2002, Bruton et al., 2005, Preskorn et al., 2004). Pargyline and a number of its acetylenic analogues had been used in the treatment of depression (Martin et al., 1975, Clark et al., 1992, Mycek et al., 1996). Most of these acetylenic analogues lack selectivity to monoaminooxidase (MAO) and therefore they interfere with hepatic metabolism of many drugs.

The antidepressant ability of these tricyclic drugs has been related to block re-uptake of nor-epinephrine and serotonin into nerve ending (Delgado and Gisvold, 1998). The observation that certain MAO inhibitors can stimulate post synaptic adrenergic neuron and, like the tricyclic antidepressant, may block the re-uptake of catecholamines (Lemke et al., 2007). In view of these pharmacological observations, it was of interest to investigate the importance of inserting an acetylenic bond within the aliphatic side chain of tricyclic dibenzazepine. In the current work we describe the synthetic programme to prepare novel hybrids of acetylenic tricyclic compounds, namely N-(4-tert-amino-2-butynyl) dibenzazepine. Their effects on pentobarbitone sleeping-time in mice were investigated. A study on selected compounds **1-7**

was carried out and had been found to prolong the sleeping time in mice as a result of their MAO inhibitory activity and the most active one was compound **1**.

MATERIAL AND METHODS:

A- Chemical methods

Melting points were determined using electrothermal melting points calibrated Thomas-Hoover melting apparatus. Infrared spectra were recorded using a Pye Unicam Sp-300 spectrophotometer. NMR spectra were taken with GE NMR-GE300 spectrometer using deuterated acetone as a solvent and tetramethysilane as a standard. Microanalyses were performed in the laboratories of the oil exploration company, Iraq and were carried out with Yanagimoto C H N Corder MT-5.

Starting materials:
Propargyl tosylate was prepared from the reaction of p-toluene sulfonyl chloride and propynyl alcohol by a method previously described (Louger et al 1964 and Yadav et al. 2003).

Preparation of N-(2-propynyl) 5H-dibenz (b,f) azepine 1:

Method A:

To a stirred solution of iminostilbene (0.5g, 2.6 mmol) in dry dimethylformamide (20 ml) and unhydrous sodium bicarbonate (0.5g, 4.32 mmol), propargyl bromide (2.6 mmol) was added dropwise. The mixture was refluxed for 2 hrs. After cooling to room temperature, the mixture was filtered and the filterate was poured into cold distilled water. The crude yellow product was crystallized from hot aqueous methanol, affording compound **1** in (84%) yield, mp: 90-92^{o}C, (reported 87-90^{o}C) (Louger et al., 1964). IR spectrum showed the following characteristic absorption bands (KBr, cm^{-1}) 3280 (≡CH), 3080 (HC=CH), 3050(ArH) 2950 (CH_2), 2100(weak,C≡C), 1650 (C=C)1550, 1500, 1450, (C=C, Ar). H-NMR spectrum demonstrated the following chemical shifts {$(CD_3)_2C=O$, δ}7.40-6.20 (multiplete, 8H, ArH), 6.15 (singlet, 2H, ArCH=CHAr) 4.50 (doublet, 2H, Ar-N-CH_2,J=2.6 Hz) 2.75(triplet,1H, C≡ C-H,J=2.6Hz).

Method B:
To stir solution of iminostilbene (0.5g, 2.6 mmol) in dry dichloromethane (10 ml) and pyridine (0.5 ml) propargyl tosylate (2.5 mmol) was added dropwise. The reaction mixture was heated at 40^{o}C for 2hrs, and left overnight at room temperature. The mixture was filtered and the filtrate was poured into cold distilled water. The crude product was separated, and crystallized from hot acetone-water, affording compound 1 in (30%) yield, m.p: 89-91^{o}C (reported 87-90^{o}C) (Louger et al., 1964). The IR and NMR spectra were consistent with that reported in method A.

Preparation of N-(4-tert-amino-2-butynyl) dibenzazepines 2-7:. N-(2-propynyl) 5H-dibenz (b,f) azepine **1** (2.2 mmol), the appropriate secondary amine (2.2 mmol) paraformaldehyde (2.2 mmole) and cuprous chloride (catalytic amount) in peroxide-free dioxane (20 ml) was heated at 70^{o}C for 3 hrs. After cooling the mixture was filtered and ice-water (50 ml) was added to the filtrate.

The crude products were collected and crystallized from the appropriate solvent. Yields, melting points and elemental analysis are shown in table 1 and 2.

The IR spectra showed the following absorption bands (KBr, cm^{-1})3280 (HC≡C-), 3050 (ArH), 2950, 2850 (CH_2), 2100 (weak,C≡C), 1650 (Ar-C=C-Ar), 1550, 1500, 1460, (C=C-Ar). The H-NMR spectrum provided the following chemical shifts {$(CD_3)_2C=O$,δ}, 7.40-6.60 (multiplete, 8H, ArH), 6.15 (singlet, 2H, ArCH=CHAr), 4.50 (triplet,2H, Ar-N-CH_2, J=2.2Hz)3.25 (triplet, 2H,C≡C-CH_2-N,J=2.2Hz).Other signals in NMR spectra were consistent with various protons in the secondary amines**. B. Pharmacological methods:** Group of mice were treated with daily i.p injections of these tricyclic acetylenic compounds **1-7**, at three levels (6.5, 12.5 and 25 mg/kg) for five days. One hour after the fifth daily injection, hypnosis was induced through i.p. injection of sodium pentobarbitone (50mg/kg). The duration of hypnosis (sleeping-time) was considered as the period of the time that the animals slept on their backs. The animals were considered awake upon righting three times in 30 seconds. The prolongation of hypnosis was compared to that of a control group received normal saline (i.p), and another received pargyline (20mg/kg, i.p.) for five days which were considered as positive control.

Results

The target compounds **1-7** were synthesized as illustrated in Fig 1.

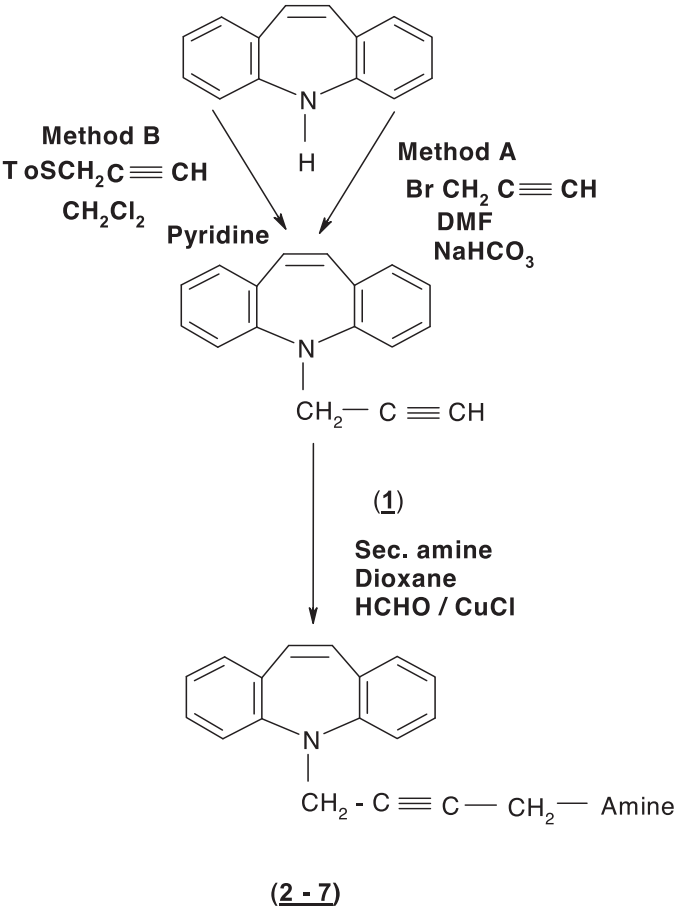
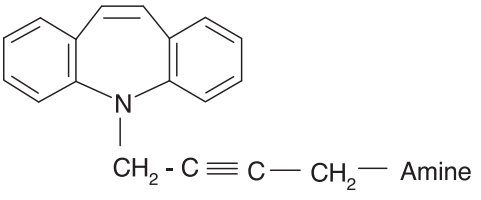


Fig. 1: Steps of the synthesis of N-(4-tert-amino-2-butynyl) dibenzazepine.

Amine= diethylamine; 2,2,6,6-tetramethyl piperidine; 2,6-dimethylpiperidine; pyrrolidine; morpholine; perhydroazocine.

The physical and analytical data of the prepared compounds are listed in tables (1) and (2).

Table 1. Physical-chemical data for N-(4-tert-amino-2-butynyl) dibenzazepine.



Compound	Am	Mp °C	Yield %	Formula [a]	(RS)[b]
1	-	90-92	84	$C_{17}H_{13}N$	Aqueous methanol
2	Diethylamine	40 - 43	66.2	$C_{22}H_{24}N_2$	Aqueous ethanol
3	2,2,6,6-dimethylpipridine	130 -133	65	$C_{27}H_{32}N_2$	Aqueous acetone
4	2,6-dimethylpipridine	120 -122	71.5	$C_{22}H_{28}N_2$	Aqueous ethanol
5	Pyrrolidine	80 - 82	52	$C_{22}H_{22}N_2$	Aqueous ethanol
6	Morpholine	84 - 86	55	$C_{22}H_{22}N_2O$	Aqueous acetone
7	Perhydroazocine	66 - 68	57.5	$C_{25}H_{28}N_2$	Aqueous acetone

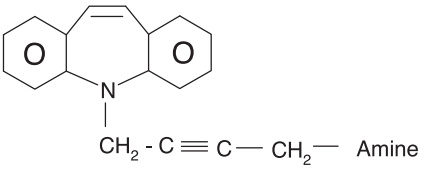
a. All compound were analyzed for C, H and N: the results had a maximum deviation of ±0.4 from theoretical values (table2).
b. Crystallization solvent.

Table 2. Elemental analysis data for compounds (1-7)

Compound	Molecular formula	% calculated			% found		
		C	H	N	C	H	N
1	$C_{17}H_{13}N$	88.31	5.63	6.06	88.67	5.68	6.43
2	$C_{22}H_{24}N_2$	83.54	7.59	8.86	83.76	7.33	8.44
3	$C_{27}H_{32}N_2.(1/2H_2O)$	82.44	8.39	7.42	82.01	8.28	7.12
4	$C_{25}H_{28}N_2$	84.27	7.87	7.87	84.72	7.56	8.21
5	$C_{22}H_{22}N_2.(1/2\ H_2O)$	81.73	6.81	8.67	81.29	6.38	8.33
6	$C_{22}H_{22}N_2O$	80.00	6.67	8.48	79.83	6.93	8.81
7	$C_{25}H_{28}N_2.(1/2\ H_2O)$	82.19	7.95	7.67	81.79	8.16	7.59

The IR and NMR spectra were consistence with the assigned structures as described in the experimental part.
The effect of the new compounds **1-7** and pargyline on pentobarbitone sleeping-time in mice are presented in table (3).

Table 3. Effects of compounds 1-7 on the pentobarbitone sleeping-time in mice[a].



Compound No.	Dose mg / kg	Time of sleeping(min) (mean ± S.C.M.)
1	6.5	68.6* ± 6.6
	12.5	72.2* ± 5.2
	25	78.2* ± 7.2
2	6.5	No sleeping
	12.5	20.6 ± 7.4
	25	22.0 ± 7.2
3	6.5	No sleeping
	12.5	21.6 ± 7.6
	25	22.6 ± 8.7
4	6.5	No sleeping
	12.5	21.6 ± 7.6
	25	28.0 ± 7.2
5	6.5	22.6 ± 8.7
	12.5	36.2* ± 9.9
	25	47.3* ± 9.9
6	6.5	24.4* ± 6.6
	12.5	37.2* ± 3.4
	25	42.2* ± 4.6
7	6.5	28.4 ± 4.8
	12.5	36.2* ± 8.3
	25	44.0* ± 4.5
Pargyline [c]	20	41.5* ± 13.2
Control [b]	Saline	22.2 ± 6.3

a. All experiments involved (8) animals per group, each group of mice were treated with daily I.P. injections of compound **(4 – 7)** for five days. b. Control animals received normal saline injections (I.P.) c. Animals received pargyline (20 mg / kg I.P.) were considered as positive control. * Significantly different from control P=0.001 students t-test.

DISCUSSION

The title compounds **2-7** were prepared by the method shown in Fig 1. N-(2-propynyl) 5H-dibenz [b,f] azepine **1** was prepared either from the reaction of 5H-dibenz [b,f] azepine (iminostilbene) with propargyl bromide in DMF using $NaHCO_3$ as a base or alternatively from reaction of iminostilbene with propargyl tosylate in dichloromethane in the presence of

pyridine (Louger et al., 1964). It should be indicated that alkylation with propargyl bromide afforded a higher yield and purer product than that with propargyl tosylate. The Mannich reaction of **1** with paraformaldehyde and the selected secondary amines in peroxide-free dioxane in the presence of catalytic amounts of cuprous chloride (Zuhair et al., 1991) yielded the N-(4-tert-amino-2-butynyl) dibenzazepine **2-7**. The physical and analytical data of the compounds prepared are listed in table1 and 2. The IR, NMR, spectra were consistent with the assigned structures as described in the experimental part.

Monoamine oxidase inhibitors (MAOI) and tricyclic drugs with clinically proven antidepressant activity exhibit a characteristic range of effects which can be used in screening for a new drug of the same type of activity. The potentiations of action of hypnotic drugs (barbiturate) were among these effects. The interference of (MAOI) with pentobarbitone metabolism, as measured by the duration of hypnosis were used as indication of possible antidepressant activity (Findaly et al., 1981), therefore the effects of the new acetylenic tricyclic compounds **1-7** on the prolongation of pentobarbitone sleeping-time in mice have been investigated.

The prototypical antidepressant agent pargyline was used as a reference compound. The results of the tests were presented in table (2). All the above mentioned compounds showed an increase in the duration of hypnosis induced by pentobarbitone as reflected in prolongation of the sleeping- time relative to the control animals. It is evident from table (3) that compound **1** with terminal acetylenic proton is the most active one and is approximately twice as potent as pargyline. All Mannich adducts were active in prolonging the duration of hypnosis with the exception of those containing a di-or tetra-methylated piperidine moiety **2, 3** respectively. The lack of activity of these lipophilic but bulky molecules, coupled with significant activity of lipophilic but nonbulky compound **7** and more polar morpholine derivatives **6**, indicate the steric restrictions may be more critical than lipophilic character in influencing affinity for the MAO active site.

To rule out possibility that these compounds may act as a general CNS depressant, and hence potentiate the effects of pentobarbitone sleeping-time. Compound **1** was administrated in a dose of (25mg/kg) to a group of mice and 1 hour post injection, hypnosis was induced with pentobarbitone. The animals never elicited a prolongation in sleeping-time. These results may suggest that these compounds act as (MAO) inhibitors, due to their ability to decrease the metabolism of pentobarbitone as was measured by the duration of hypnosis.

It is of interest to indicate that concurrent administration of tricyclic antidepressant and MAOI's produces a severe CNS toxicity including hyperpyrexia, convulsion and coma (Katzung, 2006; Bruton et al., 2005;Clark et al., 1992; Gossel and bricker, 1994; Findaly et al., 1981).Whereas the administration of these novel hybrids under similar conditions for five days did not produce these symptoms. These observations indicate the safe administration of these new acetylenic tricyclic compounds.

CONCLUSIONS

We may state that a terminal acetylenic group is of importance for potent MAOI activity. However, conversion of the terminal acetylenic proton into corresponding Mannich adducts frequently results in active compounds unless the terminal basic nitrogen is sterically hindered. Furthermore co-administration of there acetylenic tnicyckic compounds with other MAOI were safer than co-administration of tricyclic antidepressant with MAOI.

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تخليق مركبات استيلينية جديدة لمشتقات الحلقات الثلاثية ذات الفاعلية المؤثرة لتثبيط عمل انزيم أكسدة الأمينات

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الملخص

تم تخليق مشتقات جديدة لمركب داي بنزأزبين، ويتمثل ذلك بربط مجموعة استلينية، وهذه المشتقات الجديدة هي N (4-رباعي-الامين-2-بيوتانيل) داي بنزازبين. لقد شخصت هذه المركبات وتم التأكد من صحة تركيبها الكيمياوي من خلال تحليل العناصر وتحاليل أطياف الرنين النووي المغناطيسي والاشعة تحت الحمراء. كما تم تقييم الفاعلية البايولوجية لهذه المركبات من خلال تأثيرها على اطالة فترة النوم لدى الجرذان التي أعطيت عقار البنتوباربتون مما يدل على تداخلها مع عمل انزيم ماو الذي يقلل من أيض الفينوباربيتون. وتمثل هذه المركبات الجديدة إضافة نوعية لمثبطات إنزيم ماو المذكورة في الأدبيات .