RESEARCH PAPER

Received 16 June 1993
Indian J. Pharm. Sci., 1995, 57(5), pp. 198-202

Synthesis of 3,6-diaryl-2H, 3H, 4H, 5H, 6H-[1,3]-Oxazine-2- Thiones as Potential Anticonvulsants

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It is reported that (-NH-C) and (-C-NH-C) groups are associated with the analgesic and muscle relaxation properties. Therefore, synthesis of eight cyclic thiocarbamates, 3,6-dairly pentahydro- [1,3]-oxazine-2-thiones as potential anticonvulsant drugs have been attempted through cyclisation with thiophosgene of 1- arylamino-3-hydroxy-3-arylpropanes obtained earlier by hydride reduction of 1-arylamino-3-oxo-3-arylpropanes.

WITH a rapid advance in our knowledge of drug design and organic reaction mechanisms and availability of better synthetic organic methods, it has become now possible of synthasise better and more effective drugs with minimal toxicity, side effects and addiction potential. Earlier conclusions regarding the biosterical or chemical manipulations have also resulted in the development of closely resembling cyclised compounds such as oxazolidinediones, hydantoins and succinimides. Among these, trimethadiones, phenytoin and phensuxmide have proved to be excellent anticonvulsants. A characteristic feature of these drugs is the presence of amido or imido group as a common denominator.

It is hereby proposed to synthasise new substitued [1,3]-oxazine- 2-thiones as potential anticonvulsants derivatives which involves the following steps.

(i) Synthesis of substituted β- aminopropiophenones through Mannich reaction.

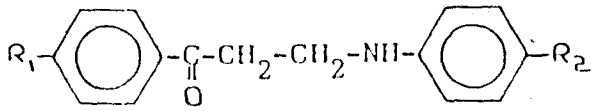
(ii) Synthesis of secondary mannich bases through amine exchange reaction of the above synthesised ketones with more basic primary amines.

(iii) Reduction of the secondary Mannich bases with sodium borohydrde.

(iv) Cyclisation of the substituted 1,3-aminopropanols obtained in the earlier step with thiophosgene to yield substituted pentahydro-[1,3]-oxazine-2-thiones.

RESULTS AND DISCUSSION

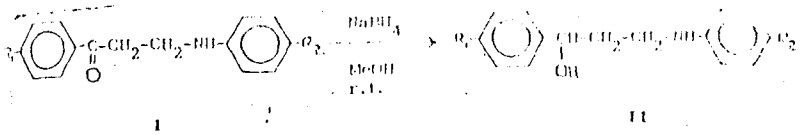
Eight new Mannich bases (I) involving aniline, p-chloroaniline, p-bromoaniline, p-nitroaniline, p-anisidine, p-toluidine, p- phenetidine and p-naphthylamine have the characteristics in agreement with those already reported in the literature and shown in **Table-1**



R_1 = Cl, R_2 = H, Cl, CH_3, NO_2, Br, OC_2H_5, OCH_3, CH_3 - C_4H_4

Reduction of the Mannich bases with sodium borohydride in methanol at room temperature with continous stirring for about 4 hrs and allowing to stand overnight at room temperature has resulted

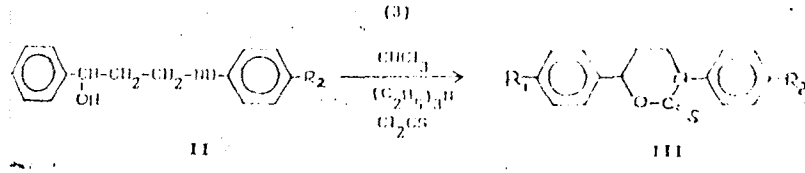
in the formation of 1-anilino/1-arylamino-3-hydroxy-3- aryl propanes (II) The physical consultants and other characteristics are reported in **table II**.



I II

R_1 = Cl, R_2 = H, Cl, Br, NO_2, OC_2H_5, OCH_3, CH_3 - C_4H_4

Cyclisation of aminocarbinols obtained above with thiophosgene in dry chloroform in presence of dry triethylamine have been successfully effected to yield (III). The physical constants and other characteristics are recorded in **table - III**.



II III

R_1 = Cl, R_2 = H, Cl,-NO_2, -Br, -CH_3,-OC_2H_5,-OCH_3,- C_4H_4

The structures of these compounds have been established through elemental analysis and study of IR, PMR and Mass Spectra.

The infra red spectra of 3,6-diaryl-pentahydro-[1,3]-oxazine-2- thiones lack the -OH and > NH absorption indicating that the cyclisation have taken place. There are lot of interactions between C-N, C-O, and C=S stretching absorptions in the region between 1400-900 cm^{-1}. However, a careful study has made it possible to identify a few absorption bands. The C-N stretching absorptions of moderate to strong intensity are noticed at 1296- 1275 cm^{-1}. The C-O stretching absorptions of strong to weak intensity are found between 1180-1020 cm^{-1}. The C=S stretching absorptions are observed at 1330-1315, 1225-1210 and 985-940 cm^{-1}. The characteristic absorption bands due to 1,4-disubstitution on aromatic rings are found at 830-800 cm^{-1} apart from C-H bending absorptions.

The PMR spectra also lack the signal due to -NH and -OH protons implyng that cyclisation of aminocarbinols wth thiophosgene has taken place. Moreover, the relative resonance frequency of the benzylic proton is raised to a higher δ value from observed in the corresponding carbinol amines to 4.7-5.4 signifying the deshielding effect of oxygen in the ring which is further attached to a thione group and also contribute to shielding to some extent. The protons of the methylene adjacent to the nitrogen atom which is further attached to a thione group also appear at higher δ values 3.5-4.0 than those of the corresponding carbinols again because of increased deshielding effect. Similarly relative proton resonance of α-methylene proton adjacent to benzylic group has also been raised to higher δ values 2.3-2.6 in the case of 6- (4-chlorophenyl)-oxazine derivatives due to increased deshielding.

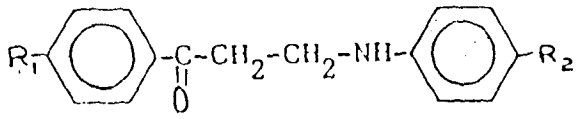
The mass spectra of the same compound shows the M^+ ion peak at m/z 303 consistant with the molecular formula of the same compound and the base peak in 100% abudance appeared at 119.

The structures of Mannch bases and their reduced products were also confirmed on the basis of their IR, PMR and Mass spectra. The mass spectrum of1-(4-chloroanilion)-3-oxo-3-(4-chlorophenyl)-propane shows M^+ ion peak at m/z 294 consistant with molecular formula of this Mannich base. The M^+ ion undergoes cleavage of the carbon-carbon bond adjacent to the nitrogen atom to yield an ion $(C_7H_7NCl)^+$ in 100% abundance (base peak) with loss of C_8H_6OCl fragment as a radical. The reduced product of the same compound shows the M^+ ion peak at m/z 296 in confirmity with its molecular formula. The M^+ ion undergoes homolytic fission of the carbon-carbon bond adjacent to nitrogen atom leading to the formation of iminium ion $(C_7H_7NCl)^+$ m/z 140 in 100% abundance (base peak).

EXPERIMENTAL

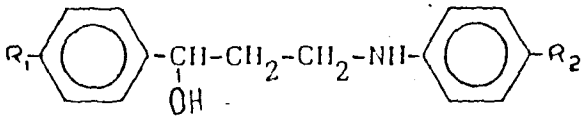
All the melting points are uncorrected. IR spectra were run on Backmann's IR-20 spectrophotometer,

Table - 1



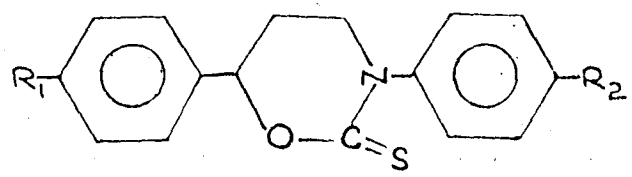
Sr. No.	Substituents		Nature	M.P. (°C)	%Yield
	R_1	R_2			
1.	Cl	-H	Creamy Crystals	124	96.7
2.	Cl	-Cl	White Crystals	118	71.3
3.	Cl	-Br	Brownish Crystals	11.5	68.3
4.	Cl	$-NO_2$	Yellow Crystals	157	96.8
5.	Cl	$-CH_3$	White Crystals	150	95.0
6.	Cl	$-OC_2H_5$	Brown Crystals	130	90.3
7.	Cl	$-OCH_3$	White Crystals	154	95.0
8.	Cl	$-C_4H_4$	Grey Crystals	162	53.0

Table-II



Sr. No.	Substituents		Nature	M.P. (°C)	%Yield
	R_1	R_2			
1.	Cl	-H	White Crystals	71	68.07
2.	Cl	-Cl	White Crystals	60	93.3
3.	Cl	-Br	Brownish Crystals	80	87.0
4.	Cl	$-NO_2$	Pale Yellow Crystals	85	87.0
5.	Cl	$-CH_3$	White Crystals	95	92.0
6.	Cl	$-OC_2H_5$	White Crystals	78	86.0
7.	Cl	$-OCH_3$	White Crystals	75	96.0
8.	Cl	$-C_4H_4$	Creamy Crystals	98	59.0

Table-III



Sr. No.	Substituents		Chemical Name	Nature	M.P. (°C)	%Yield
	R_1	R_2				
1.	Cl	H	3-Phenyl-6-(4-chlorophenyl) -2H,3H,4H,5H,6H-[1,3]-oxazine-2-thione	White Crystals	168	68
2.	Cl	Cl	3-(4-Chlorophenyl)-6-(4-chlorophenyl)-2H,3H,4H,5H,6H-[1,3]-oxazine-2-thione	White Crystals	195	62.8
3.	Cl	Br	3-(4-Bromophenyl)-6-(4-chloro-phenyl) -2H,3H,4H,5H,6H-[1,3]-oxazine-2-thione	Brownish Crystals	148	79.0
4.	Cl	NO_2	3-(4-Nitrophenyl)-6-(4-chlorophenyl) -2H,3H,4H,5H,6H-[1,3]-oxazine-2-thione	Yellow Crystals	188	68
5.	Cl	CH_3	3-(4-Methylphenol)-6-(4-chlorophenyl) -2H,3H,4H,5H,6H-[1,3]-oxazine-2-thione	Wheatish Crystals	138	61
6.	Cl	OCH_3	3-(4-Methoxyphenyl)-6-(4-chlorophenyl) -2H, 3H, 4H, 5H, 6H-[1,3]-oxazine-2-thione	Grey Crystals	154	72
7.	Cl	OC_2H_5	3-(4-Ethoxyphenyl)-6-(4-chlorophenyl) -2H,3H,4H,5H,6H-[1,3]-oxazine-2-thione	White Crystals	132	59
8.	Cl	C_4H_4	3-(2-Naphthyl)-6-(4-chlorophenyl) -2H,3H,4H,5H,6H-[1,3]-oxazine-2-thione	Brown Crystals	145	66

PMR on Varain-A-60 spectrophotometer and mass spectra on MS-12 spectrophotometer.

(i) Synthesis of Mannish Bases

Mannich bases were prepared by simplified procedure[1,2,3] and were reduced as per literature procedure[4] and data reported in Table-1.

(ii) Reduction of Mannich Bases

A typical procedure adopted is described as for the synthesis of 1-anilino-3-hydroxy-3-(4-chlorophenyl)-propane. For this to a solution of 1-anilino-3-oxo-3-(4-chlorophenyl)-propane (13.00 gms, 0.05 mole) in methanol (200 ml), sodium borohydride (2.08 gm, 0.055 mole) was added pinch by pinch with constant magnetic stirring over a period of 2 hrs. The mixture was allowed to stand overnight at room temp. After evaporating the solvant, the residue was diluted with small quantity of water and extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate. The solvent was pulled out under reduced pressure to yield a solid residue which was recrystallised from benzene- petroleum ether mixture to give white crystalline product (yield 68.07%).

Other substituted products were also synthasised in the same way and data is recorded in Table-II.

(iii) Cyclisation of Reduced Product with Thiophosgene

A typical procedure is same as described for the synthesis of 3-phenyl-6-(4-chlorophenyl)-2H, 3H, 4H, 5H, 6H, -[1,3]-oxazine-2- thiones. For this 1-anilino-3-hydroxy-3-(4-chlorophenyl)- propane (5.23 gms, 0.02 mole) dissolved in dry chloroform (25.00 ml) was taken in a round bottom flask fitted with a two way head carrying reflux condensor and dropping funnel. Triethylamine (5.6 ml, 0.04 mole) was added to it and contents were cooled in an ice bath. A solution of thiophosgene (1.5 ml, 0.02 mole) in dry chloroform (20.00 ml) was added dropwise with constant stirring. The reaction mixture was kept overnight at room temp. and washed with distilled water to remove trethylamine hydrochloride formed during the reaction. After drying over anhydrous sodium sulphate, the solvant was distilled off under reduced pressure to yield a thick mass which was recrystallised from benezene-petroleum ether to give white crystalline product (yield 68.00%).

Other substituted 3.6-diaryl-pentahydro-[1,3]-oxazine-2-thiones were also synthesised in the same way and data is reported in table-III.

REFERENCES

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4. M. Bockmuhl, G. Ehrhart, O. Eisleb and L. Stein, U.S. Pat, 1948, 24446522; **Chem. Abstr**, 1949, 43, 1810.