

Synthesis and Biological Activities of Substituted-1-Tetralone Derivatives: Part-II

A. V. NAIDU and M.A. DAVE*

Department of Chemistry

*K.J. Somaiya College of Science and Commerce
Vidyanagar, Vidyavihar, Mumbai-400 077, India*

2-Amino-4,5-dihydronaphtho-[1,2-d]-thiazole was condensed with salicylaldehyde to get Schiff base, it was reduced and cyclized to get 2H-3-(4,5-dihydronaphth-[1,2-d]-thiazole)-3,4-dihydro-1,3-benzoxazine. The Schiff base with DMSO-I₂-H₂SO₄ gave 2H-3-(4,5-dihydronaphtho - [1,2-d]-thiazole) - 3,4-dihydro - 1,3-benzisoxazole. Synthesis of 6-methoxy methyl naphtho-[1,2-d][1,2,3]-thiazole-4-carboxylate, 6-methoxynaphtho-[1,2-d][1,2,3]-thiazole-4-hydrazo-carbonyl and 6-methoxynaphtho-[1,2-d][1,2,3]-thiazole-4-arylidene hydrazocarbonyl prepared from the starting compound 3-carbomethoxy-7-methoxy-1-tetralone.

INTRODUCTION

A large number of substituted benzisoxazoles, benzoxazoles and substituted benzoxazines are known for various biological activities¹. Benzisoxazoles are prepared² by heating *o*-bromobenzophenone and acetophenone oxime acetate by the action of DMSO-I₂-H₂SO₄ system on phenolic Schiff bases.³ The phenolic Schiff bases on oxidative cyclisation by Ag₂O and CuCl₂ in nitrobenzene gave substituted benzoxazole.⁴ Benzoxazine was prepared by reducing phenolic Schiff bases followed by cyclisation employing formaline.⁵

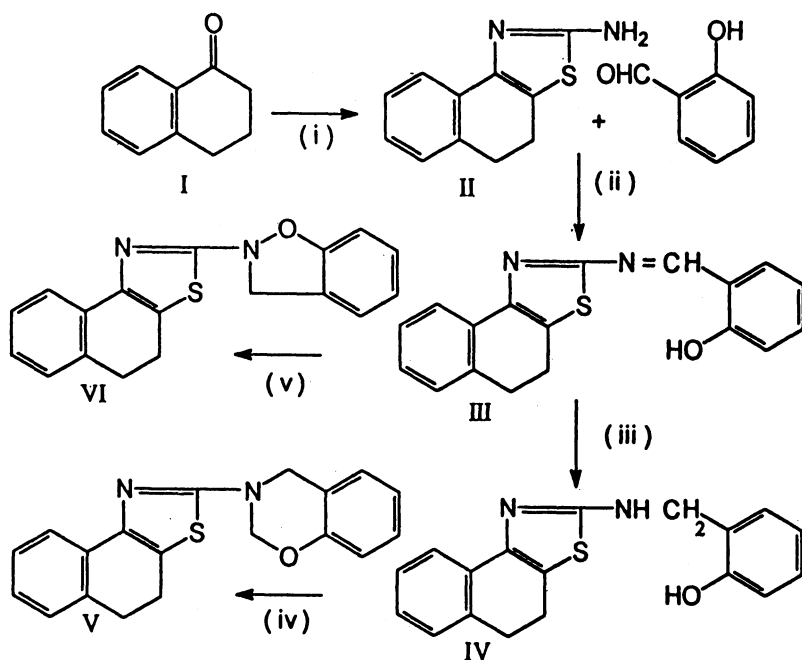
Various 1,2,3-thiadiazole derivatives are of interest for pharmaceutical use,⁶⁻⁹ as well as useful intermediates in the area of organic synthesis.¹⁰ 1,2,3-Thiazole derivatives were synthesized by the method developed by Hurd and Mori,¹¹ a one pot reaction by the treatment of N-acyl or N-tosyl hydrazones bearing an adjacent α -methyl or α -methylene group with thionyl chloride.

In continuation of our studies on substituted 1-tetralones, with a view to synthesis of analogous compounds with possible antibacterial properties, benzisoxazole derivatives and benzoxazine derivatives were prepared using 1-tetralone. We were interested in the synthesis of 6-methoxynaphtho-[1,2-d][1,2,3] thiazole-4-hydrazocarbonyl and its hydrazones, the antibacterial properties of the tricyclic 1,2,3-thiazole derivatives had been screened against different types of bacteria.

1-Tetralone (I) was condensed with thiourea and iodine by Dodson-King Method¹² and the resulting 2-amino-4,5-dihydronaphtho-[1,2-d]-thiazole (II) was then treated with salicylaldehyde to get the corresponding Schiff base (III), which was reduced by NaBH₄ to give IV. The compound IV was treated with formalin

to get the corresponding benzoxazine derivative V. The Schiff base with DMSO-I₂-H₂SO₄ gave a brown solid which showed negative ferric chloride test indicating the absence of hydroxyl group.

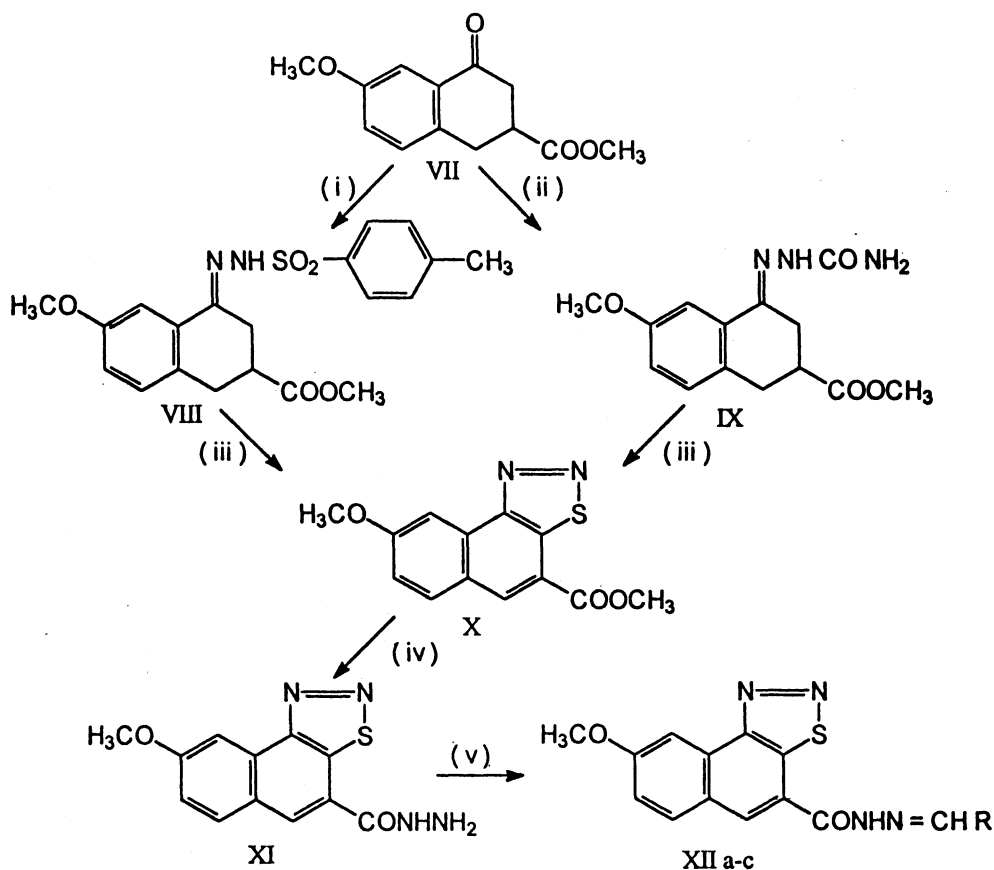
3-Carbomethoxy-7-methoxy-1-tetralone¹³ (VII) was treated with *p*-toluene sulphonyl hydrazide to get the corresponding hydrazone VIII. Cyclisation of VIII using thionyl chloride gave the naphtho thiaziazole derivative X. Compound X was also obtained by the cyclisation of 3-carboxy-7-methoxy-1-tetralone semi-carbazone¹² IX using thionyl chloride. X was condensed with hydrazine hydrate to get the corresponding hydrazocarbonyl (XI). Hydrazones XII were obtained from the condensation of XI with aldehydes (benzaldehyde, pyridine-3-aldehyde, thiophene-2-aldehyde).



- (i) Thiourea, Iodine
(ii) Ethanol
(iii) Sodium borohydride
(iv) Formalin

(v) DMSO-I₂-H₂SO₄

Compound No.	m.p. °C	Colour	Yield %	Formula
III	128-30	bright yellow	73.68	C ₁₈ H ₁₄ N ₂ OS
IV	178-80	colourless	94.16	C ₁₈ H ₁₆ N ₂ OS
V	111-12	colourless	60.62	C ₁₉ H ₁₆ N ₂ OS
VI	208-09	pale yellow	10.20	C ₁₈ H ₁₄ N ₂ OS



- (i) p-toluene sulphonyl hydrazide
 (ii) Semicarbazide hydrochloride
 (iii) Thionyl chloride
 (iv) Hydrazine hydrate
 (v) Aryl aldehydes

- a-Ph.
 b-2-thiophene
 c-3-pyridine

Compound No.	m.p. $^{\circ}\text{C}$	Colour	Yield (%)	Formula
VIII	265-66	colourless	88.55	$\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$
X	198-99	colourless	using methods (i) (ii)	
			70.20 46.42	
XI	224-26	colourless	68.96	$\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$
XII a	232-34	light brown	65.19	$\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_2\text{S}$
XII b	228-30	light brown	85.95	$\text{C}_{19}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$
XII c	240-41	light brown	79.89	$\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_2\text{S}$ $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2\text{S}_2$

EXPERIMENTAL

All melting points of the compounds synthesized are uncorrected. Microanalyses of the compounds were carried out on a Coleman IR spectra (KBr) were recorded on a Perkin-Elmer, Paragon-2000 instrument. NMR spectra were recorded on an AMX-500 Bruker (500 Hz) and Varian instrument (300 Hz.) using TMS as the internal standard. All the compounds gave satisfactory C, H and N analyses.

2-[N-(2-Hydroxyphenyl)-methylidiny]-amino-4,5-dihydronaphtho [1,2-d] -thiazole (III)

A mixture of II (1.94 g, 0.01 mol) and salicylaldehyde (1.24 g, 0.01 mol) in absolute ethanol (25 mL) was refluxed for 4 h. The reaction mixture was cooled and the separated solid was crystallised from ethanol.

2-(2-Hydroxybenzal-amino)-4,5-dihydro naphtho [1,2-d] thiazole (IV)

A mixture of III (0.612 g, 0.002 mol) and sodium borohydride (0.3 g, 0.088 mol) in absolute methanol (25 mL) was stirred at room temperature for 1 h. The reaction mixture was cooled and poured into cold water and the separated solid was crystallised from ethanol.

2H-3-(4,5-Dihydro naphtho-[1,2-d] thiazole)-3,4-dihydro-1,3-benzoxazine (V)

A mixture of IV (0.616 g, 0.002 mol) and formalin (1 mL, 37%, 0.01 mol) in absolute ethanol (5 mL) was refluxed for 5 h. The reaction mixture was cooled and poured into cold water; the separated solid was crystallised from ethanol.

2H-3-(4,5-Dihydronaphtho-[1,2-d]-thiazole)-1,3-benzisoxazole (VI)

To a mixture of III (3.06 g, 0.01 mol) in DMSO (40 mL) was added a drop of concentrated sulphuric acid followed by a small crystal of iodine. The reaction mixture was warmed on a steam bath for 1h. The yellow solid separated on pouring the reaction mixture into cold water. The solid was filtered and crystallised from ethanol.

6-Methoxy, methyl-1,2,3,4-tetrahydro-4-{2-[(4-methyl-phenyl)-sulfonyl]-2-hydrazinyl-1-yliden}-2-naphthalene carboxylate (VIII)

A mixture of VII (2.34 g, 0.01 mol) and *p*-toluene sulphonyl hydrazide (1.86 g, 0.01 mol) in absolute methanol (15 mL) was refluxed for 4 h. The reaction mixture was cooled and the separated solid was crystallised from ethanol.

6-Methoxy, methyl-naphtho [1,2-d][1,2,3]-thiadiazol-4-carboxylate (X)

Method 1: VIII (1.27 g, 0.01 mol) dissolved in 10 mL dichloromethane was treated with thionyl chloride (4.7 mL, 0.0064 mol) and stirred at room temperature for 18 h. Thionyl chloride was removed under pressure and the oily residue was chromatographed on 30 g silica gel using benzene 100% giving colourless crystals of X.

Method 2: IX (0.77 g, 0.03 mol) was added in portions to thionyl chloride (2.35 mL, 0.0032 mol) over a period of 0.5 h. The temperature was maintained between 0–5°C. The reaction was gradually warmed to room temperature and kept overnight. Chloroform was added to the reaction mixture followed by cold saturated sodium bicarbonate solution. The organic layer separated was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The solid obtained was crystallised from ethanol.

The compounds synthesized from the above two methods were found to be identical in all respects (TLC, IR and m.p.).

6-Methoxy, methyl naphtho-[1,2-d][1,2,3]-thiadiazol-4-hydrazocarbonyl (XI)

A mixture of X (0.5 g, 0.0018 mol) and hydrazine hydrate (1 mL, 98%, 0.002 mol) in absolute ethanol (15 mL) was refluxed for 4 h. The reaction mixture was cooled, the separated solid was crystallised from ethanol.

6-Methoxy, methyl naphtho-[1,2-d][1,2,3]-thiadiazol-4-arylidene hydrazocarbonyl (XII a-c)

A mixture of (XI) (0.274 g, 0.001 mol) and aryl aldehyde (0.001 mol) in absolute ethanol (5 mL) was refluxed for 4–5 h. (TLC). The reaction mixture was cooled and the separated solid was crystallised from ethanol.

RESULTS AND DISCUSSION

The IR spectra of 2-[N-[(2-hydroxy phenyl)-methylidynyl]-amino-4,5-dihydro naphtho-[1,2-d] thiazole (III) showed the absorption band in the region of 3431 cm^{-1} due to —OH stretchings. The azomethine group —CH=N showed the absorption band at 1612 cm^{-1} . The IR spectra of 2-(2-hydroxy benzal amino)-4,5-dihydro naphtho-[1,2-d]-thiazole (IV) showed the absorption band in the region of 3431 cm^{-1} due to —OH stretching. The absence of the peak in the region of 1620–1610 cm^{-1} of azomethine group —CH=N confirms that reduction has taken place at the double bond. The NMR spectra of 2H-3-(4,5-dihydro naphtho-[1,2-d]-thiazole)-3,4-dihydro-1,3-benzoxazine (V) showed signals in the region of δ 2.4–2.9 ppm of eight methylene protons. Aromatic protons showed multiplet at δ 7.1–7.4 ppm of eight protons. The NMR spectra of 2H-3-(4,5-dihydro naphtho-[1,2-d] thiazole)-1,3-benzisoxazole (VI) showed signals in the region of δ 2.8–3.2 ppm of six methylene protons. Aromatic protons showed multiplet at δ 7.0–7.8 ppm of eight protons. The IR spectra of 6-methoxy, methyl naphtho-[1,2-d][1,2,3]-thiadiazol-4-carboxylate (X) showed the absorption band in the region of 3208 cm^{-1} due to —NH stretchings. The ester carbonyl showed the peak at 1738 cm^{-1} . The NMR spectra of X showed signals in the region of δ 4.0 ppm of six protons (methoxy and ester groups). Aromatic protons showed multiplet at δ 7.5–8.5 ppm of four protons. The IR spectra of 6-methoxy, methyl naphtho-[1,2-d][1,2,3]-thiadiazol-4-hydrazocarbonyl (XI) showed the absorption band in the region of 3307 cm^{-1} due to —NH stretchings. The amido group showed the absorption band at 1630 cm^{-1} . The IR spectra of 6-methoxy, methyl

naphtho [1,2-d][1,2,3] thiadiazol-4-arylidene hydrazocarbonyl (XII a-c) showed the absorption band in the region of 3300–3200 cm^{-1} due to —NH stretchings. The amido group showed the absorption band at 1640–1630 cm^{-1} . The azomethine group —CH=N showed the absorption band in the region 1615–1610 cm^{-1} .

Antibacterial activity

All the compounds were subjected to M.I.C. (minimum inhibitory concentration) test. Strains of the following bacteria were used: *Staphylococcus aureus*, *Escherichia coli*, *Salomonella typhi*, and *Klebsiella pneumoniae* and none of them showed any significant antibacterial activity.

REFERECES

1. J. Sengupta, *Indian J. App. Chem.*, **29**, 3 (1964); L. Muslin, W. Roth and H.H. Erlenmeyer, *Helv. Chim. Acta*, **36**, 36 (1953); S.P. Hiremath and B.H.M. Mruthyunjayaswamy, *Indian J. Chem.*, **16B**, 491 (1975).
2. K.A. Thakur and B.M. Bhawal, *J. Indian Chem. Soc.*, **54**, 874 (1977).
3. P.D. Lokhande and B.J. Ghiya, *J. Indian Chem. Soc.*, **68**, 412 (1991).
4. M. Yoshifuji, T.N. Kawashima and N. Inamoto, *Heterocycles*, **11**, 133 (1978); M.K. Raja and N.V. Rao, *Acta Cienc. Indica*, **10C**, 185 (1984).
5. A. Sammor and A.F.M. Fahmy, *Indian J. Chem.*, **11**, 222 (1973).
6. B.K. Shanthaveerappa, G. Rajshekhar and B.H.M. Mruthyunjayaswamy, *Indian J. Chem.*, **37B**, 453 (1998).
7. T.C. Briton, T.J. Lobl and C.G. Chidester, *J. Org. Chem.*, **49**, 4773 (1984).
8. G.S. Lewis and P.H. Nelson, *J. Med. Chem.*, **22**, 1214 (1979).
9. E.W. Thomas, E.E. Nishizawa, D.C. Zimmermann and D.J. Williams, *J. Med. Chem.*, **28**, 444 (1985).
10. P. Stanetty, M. Kremslehner and M. Mullner, *J. Heterocyclic Chem.*, **33**, 1759 (1996).
11. C.D. Hard and R. J. Mori, *J. Am. Chem. Soc.*, **77**, 5359 (1955).
12. R.M. Dodson and L.C. King, *J. Am. Chem. Soc.*, **67**, 2242 (1945).
13. K.N. Campbell, J.A. Cell and B.K. Campbell, *J. Am. Chem. Soc.*, **75**, 4685 (1953).

(Received: 10 December 1999; Accepted: 25 January 2000)

AJC-1981