Vol.3 Nol. 1,2
Winter&Spring 1992

STUDIES ON SPIROHETEROCYCLES: SYNTHESIS OF NEW SPIRO 4-THIAZOLIDINONES AS POSSIBLE BIODYNAMICS

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Abstract

Spiro-4- thiazolidinones have been synthesized by the cyclocondensation of phthalazinyl hydrazones with cyclic ketones and substituted mercapto acetic acids. Compounds were screened for their antibacterial, antifungal and antihypertensive activity. The combined elemental analyses and spectroscopic data prove the authenticity of the synthesized compounds.

Introduction

As an extension of our earlier work on the synthesis of 4-thiazolidinones containing biologically active phthalazine moiety [1], we have now investigated in detail the synthesis of phthalazinyl hydrazones with mercapto acetic acids.

The literature survey reveals a wide range of pharmacological properties of spiro-4-thiazolidinones [2-7]. Phthalazine derivatives also possess wide therapeutic activity [8-15]. These observations prompted us to synthesize the spiro-4-thiazolidinones of type (III). The condensation of 1,4-bis hydrazino phthalazine with cyclic ketones afforded hydrazones (II), which on further treatment with mercapto acetic acids in the presence of anhydrous zinc chloride gave corresponding spiro-4-thiazolidinones. The structural assignment of these products is based on elemental analyses and IR, NMR spectral data. Biodynamics of these products have been studied.

Keywords: Spiro-4- thiazolidinones, Antibacterial, Antifungal, Antihypertensive

Biodynamic Activity

(a)Antimicrobial Activity:

The antimicrobial screening was carried out using cup plate method [16] at 50 μg concentration against **S. aureus, S. citreus, E. coli, Ps. flourescens** and the fungus **C. albicans & A. flavus.** Under identical conditions the standard antibiotics: Ampicillin showed a zone of inhibition 16-22 mm, Chloramphenicol 15-25 mm, Norfloxacin 17-33 mm, Tetracycline 21-30 mm against various strains of micro-organisms. It was observed that all the compounds were good to moderately active. Maximum activity was observed in compounds having (along with zone of inhibition) X=H, n=3 (22 mm), and X=CH_3 , n=4 (20 mm); against **S. aureus,** X=H, n=1 (21 mm) against **S. citreus,** X=CH_3, n=4 (28 mm) and X =CH_2 COOH, n=1 (30 mm) against **E. coli,** X =CH_2, COOH, n=2 (32 mm) and n=3 (33 mm) against **Ps. flourescens**; while spiro-4-thiazolidinones of type-II were less active against **A. flavus.**

(b) Antihypertensive Activity:

The CVS activity of all compounds was carried out

in anaesthetised (Phenobarbital sodium 35.0 mg/kg i.P.) cats (3-4 kg) of either sex. The blood pressure and respiration were recorded on a Kymograph and Marey's tambour, after connulating the right common carotid artery and the trachea respectively. The contractions of the nictitating membranes due to stimulation of the cervical sympathetic nerve fibres were also recorded. Responses to intravenous adrenaline (2-3 μg), histamine (1-2 μg), acetylcholine (0.5-1 μg) and isoprenaline (0.5-1 μg) on the blood pressure was recorded before and after the administration of the compounds. All test substances and standard agents were administered through an indwelling polythene cannul in the right femoral vein.

The tested compounds did not produce any significant effect on the blood pressure or any of the response to standard autonomic agents. Moreover, compound No. III_e, III_f, III_g were active against all the tested doses and compared with Dihydralazine hydrochloride (42 mm/Hg). At the doses of 1.0, 2.5, 5.0 mg/kg i.v., it produced a fall in b.p. of 42 mm, 46 mm and 51 mm respectively, which lasted for 2 min. Thus-CH_3 group (compd. III_{efg}) might be responsible for CVS activity. The activity of the other compounds was transitory. Thus it was observed that the derivatision of dihydralazine considerably reduce the hypotensive activity of the parent compounds.

Experimental Section

General remarks: Melting points were determined in open capillary tubes and are uncorrected. Hemogenicity of the compounds was routinely checked by TLC on Silicagel-G.

IR (KBr) spectra were recorded using Shimadzu-435 IR spectrophotometer. NMR spectra were recorded on a Varian CFT-20 spectrometer and chemical shift are in (δ) ppm relative to $(CH_3)_4Si$. Elemental analyses are quite comparable with their structures. In all cases analytical values for elements were ± 0.05 % of theoretical values. Physical constants are recorded in table-1.

Phthalazinyl hydrazones of cyclic ketones II: General procedure (Table -1) :

1,4-Bis hydrazino phthalazine (1.9 gm, 0.01 m) in ethanol (25 ml) was refluxed for 3 hrs with cycloheptanone (2.24 gm, 0.02 m). After evaporation of the solvent to one third of its volume under vacuum yielded the products. It was crystallised from ethanol to give 3.6 gm (65%) of II_c, m.p. 89°C;

IR (KBr) II_c: 3350 (-NH); 2900, 2850 (-CH_2); 1615 (-N= C-); 1590, 1510 cm^{-1} (C= C + C= N).

NMR ($DMSOd_6$) δ ppm II_c: 1.63 (8H, s, $2CH_2$); 2.40 (8H, s, $2CH_2$); 2.70 (8H, s, $2CH_2$); 7.2-8.4 (4H, M, Phthalazine protons); 10.5 (2H, s(br.) 2NH).

II_c Anal. calcd. for $C_{22}H_{30}N_6$ C, 70.86; H, 7.08; N, 22.04; Found: C, 70.75; H, 6.95; N , 21.99%).

1,4- Bis(2', 2"- spiro cyclopentano/ cyclohexano/cycloheptano/cyc - looctano 5'H/methyl - 4'- thiazolidinon - 3' - ylamino) phthalazine(III_{a-h}): General Procedure (Table-1):

A mixture of cyclohexano phthalazinyl hydrazone (4.98 gm, 0.01 m) thioglycolic acid (3.68 ml, 0.04 m)/ thiolactic acid (4.24 ml, 0.04 m) and anhydrous zinc chloride (1.0 gm) was heated at 120°C for 10 hrs. The reaction mixture cooled and triturated with 10% sodium bicarbonate solution. The solid product separated out, which was filtered, washed with distilled water and dried. The product thus obtained was filtered through Alumina in chloroform evaporation of solvent gave productIII_b 2.6 gm (48%), m.p. 163°C and III_f 3.9 gm (52%), m.p 171°C.

IR (KBr) III_b: 3400 (NH); 2950 (CH, asym.); 2850 (CH sym.); 720 (CH); 1680, 1100, 590 cm^{-1} (C=0, C-N, C-S-C, thiazolidinone moiety respectively).

NMR (δ ppm) III_b: 1.11-3.11 (20H, m, 2C-$CH_2)_5$; 4.45 (4H, s, $2CH_2$-S); 7.28-8.82 (4H, m, Phthalazine protons); 10.9 (2H, s, 2NH). III_b Anal calcd. for $C_{24}H_{30}N_6O_2S_2$ C, 60 .87%; H, 6.52; N, 16.87, Found: C, 60.85; H, 6.50; N, 16.81%). NMR (δ ppm) III_f: 1.2-3.4 (20H, m, 2C-$(CH_2)_5$; 1.5 (d, 6H, $2CH_3$ merged with -CH_2 protons); 3.8 (q, 2H,$2CH_3$); 7.3-8.0 (4H, m, Phthalazine protons), 9.98 (2H, s, 2NH).

III_f Anal. calcd. for $C_{26}H_{34}N_6O_2S_2$ C, 58.87%; H, 5.51; N, 16.03; Found: C, 58.86; H, 5.50; N, 16.00%.

1,4 - Bis (2', 2" spiro cylcopentano/ cyclohexano/cycloheptano/ cyclooctano-5'-carboxymethyl - 4' - thiazolidinon - 3'-ylamino)phthalazine(III_{i-1}): General procedure (Table-1):

A mixture of II_c (4.98 gm, 0.01 m), thiomalic acid

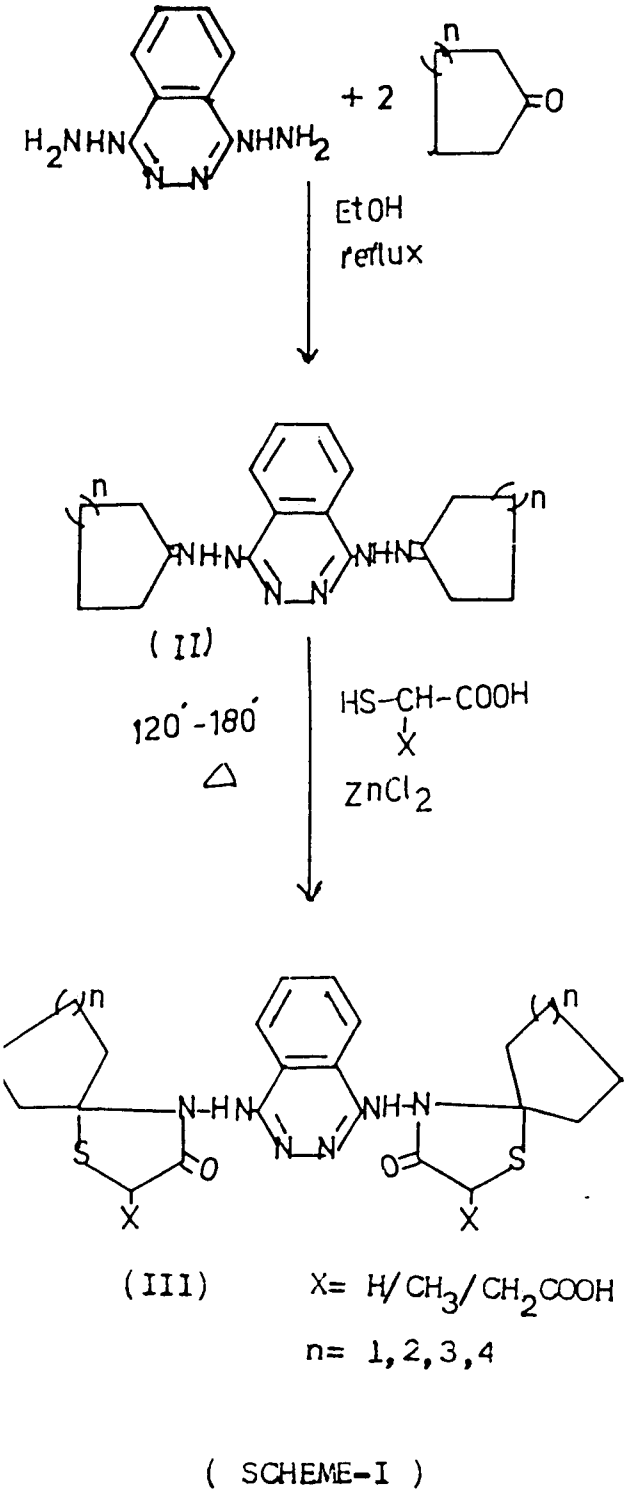
(8.82 gm, 0.03 m) and anhydrous zinc chloride (1.0 gm) was heated at 160°C for 3 hrs., the temperature was then raised to 180°C for 30 min. The product was extracted in 10% sodium bicarbonate solution and reprecipitated with dilute HCl and was filtered through Alumina in chloroform, evaporation of solvent gave the product III_j 3.7 gm (51%), m.p. 290°C. IR (KBr) III_j: 3400 (OH); 3250 (-NH); 2940 (CH, asym.); 2860 (CH sym.); 1720 (C=0); 1590 (O=C=-O); 1080 (C-N); 690 (C-S-C); 720 cm^{-1} (-CH).

NMR (δ ppm) III_j: 1.85-3.4 (20H, m, 2C-$(CH_2)_5$; 1.7 (d, 4H, 2C**H**$_2$COOH); 3.65 (t, 2H, 2CH-CH_2-); 7.0-7.85 (4H, m, phthalazine protons); 10.10 (2H, s, 2-OH); 11.21 (2H, s, 2- COO**H**).

III_j: Anal. calcd. for $C_{28}H_{34}N_6O_6S_2$ C, 60.81; H. 6.50; N, 13.75, Found: C, 60.80; H, 6.50; N, 13.70%.

Table 1- Physical constants of spiro -4- thiazolidinones II_{a-d}-III_{a-l}

Compd. No.	X	n	Molecular formula	M.P. °C	N% Found (Calc.)
II_a	-	1	$C_{18}H_{22}N_6$	138	26.01 (26.09)
II_b	-	2	$C_{20}H_{26}N_6$	175	23.90 (24.00)
II_c	-	3	$C_{22}H_{30}N_6$	89	22.19 (22.22)
II_d	-	4	$C_{24}H_{34}N_6$	101	20.61 (20.69)
III_a	H	1	$C_{22}H_{26}N_6O_2S_2$	205	17.80 (17.87)
III_b	H	2	$C_{24}H_{30}N_6O_2S_2$	163	16.81 (16.87)
III_c	H	3	$C_{26}H_{34}N_6O_2S_2$	135	15.90 (15.97)
III_d	H	4	$C_{28}H_{38}N_6O_2S_2$	187	15.05 (15.16)
III_e	CH_3	1	$C_{24}H_{30}N_6O_2S_2$	163	16.90 (16.94)
III_f	CH_3	2	$C_{26}H_{34}N_6O_2S_2$	171	16.00 (16.03)
III_g	CH_3	3	$C_{28}H_{38}N_6O_2S_2$	132	15.19 (15.22)
III_h	CH_3	4	$C_{30}H_{42}N_6O_2S_2$	65	14.40 (14.48)
III_i	CH_2 COOH	1	$C_{26}H_{32}N_6O_6S_2$	158	14.31 (14.38)
III_j	CH_2COOH	2	$C_{28}H_{34}N_6O_6S_2$	290	13.70 (13.75)
III_k	CH_2COOH	3	$C_{30}H_{40}N_6O_6S_2$	129	13.10 (13.13)
III_l	CH_2COOH	4	$C_{32}H_{44}N_6O_6S_2$	168	12.58 (12.53)



(SCHEME-I)

Acknowledgements

The authors are thankful to *Dr. A. R. Parikh*, Prof. and Head, Department of Chemistry, Saurashtra University, Rajkot (India) for facilities and to *Dr. (Mrs.) H.H. Parekh*, for spectral interpretation. Our thanks are also due to the Director and Head, Pharmacological division of CDRI Lucknow for biodynamics evaluation and spectral analyses. Technical assistance of *Mr. R. M. Saxena* & *Mr. Bhartibhusan* of CDRI is also acknowledged.

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