

Synthesis and anti-convulsant study of benzylidene Rhodanine derivatives

JAGBIR GAGORIA*, KULDEEP SINGH, S.K. JAIN,
GAUTAM and ANURAG KHATKAR¹

*Institute of Pharmacy, Bundelkhand University, Jhansi - 284 128 (India).

¹Dr. K.N. Modi Institute of Pharmaceutical Education and Research, Modi Nagar (India)

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ABSTRACT

A new series of Benzylidene Rhodanine (b) have been synthesized by reaction of Rhodanine (a) and aromatic aldehydes which upon O-alkylation with different chloro- acetamides (c₁₋₄) form the final derivatives (d₁₋₄). The physical and spectral data of synthesized compounds are determined. The synthesized compounds have been screened for their anti-convulsant activity by MES method.

Keywords: - Benzylidene Rhodanine, Anti-convulsant activity.

INTRODUCTION

During the past years, considerable evidence has been accumulated to demonstrate the efficacy of Rhodanine (2-thioxo-4-thiazolidinone) derivatives. Rhodanine based molecules have been popular as small molecule inhibitors of numerous targets such as anti-convulsant agents^{1,2}, anti-diabetic agents³, anti-microbial agents⁴ and histidine decarboxylase⁵.

Dry ammonia and carbon disulphide in alcohol and ether combined to form ammonium dithiocarbamate, which react with sodium chloroacetate to form rhodanine⁶(a). Rhodanine on condensation with salicylaldehyde form o-hydroxy benzylidene rhodanine⁶(b). This key intermediate upon O-alkylation with different chloro acetamides (c₁₋₄) form final derivatives (d₁₋₄)⁷. The title compounds (c₁₋₄) have been synthesized via various amines with chloro acetyl chlorides in acetic acid⁸. The physical properties of compounds are presented in table.1 and table.2.

MATERIAL AND METHODS

All the chemicals used were AR grade and some were LR grade, procured from various chemical units like Merck, Mumbai; Qualigens, Mumbai; s.d.Fine, Mumbai and CDH-New Delhi. Melting points were determined in open glass capillaries and are uncorrected. The I.R. spectra (KBr disc) were recorded on FTIR-200 Thermo Electron Corporation. ¹H NMR spectra were recorded in DMSO using BRUKER AVANCE II 400 NMR spectrometer. The chemical shifts were expressed in δ units in ppm downfield from TMS. The purity and completion of reaction was monitored by TLC using benzene: ethyl acetate, 4:1 solvent system and silica gel-G coated on glass plates as solid support.

Synthetic study

The scheme of some benzylidene rhodanine analogues is given in Fig.1

Synthesis of rhodanine⁶ (a)

Dry ammonia passed through an ice-cooled mixture of carbon disulphide (30ml), alcohol

(24ml) and ether (24ml) for a period of about 3.5 hrs. The content of flask solidified into a pale yellow cake i.e. ammonium dithiocarbamate. This was further washed with alcohol (5ml), followed by ether (10ml). This was immediately added to a solution of sodium chloroacetate with stirring which in turn prepared by mixing of sodium hydroxide (0.5mol) and chloroacetic acid (0.5mol), the mixture was cooled to 0°C. At first the solution become dark but on further stirring mixture turned straw like. The above content then finally added to the 36ml of conc. HCl. The mixture was heated to 80°C for 2min., and then placed the flask to an ice bath for 1hr., glistening pale yellow crystals of rhodanine separated out, filtered and washed with little water and finally recrystallized from alcohol. Yield - 65%; m.p - 169°C; I.R. Data – 1713(C=O), 1185(C=S), 3091(NH), 1234(C-N), 2839(C-H).

Synthesis of o-hydroxy benzylidene rhodanine⁶ (b)

Rhodanine (0.02mol) added to the preheated 50ml glacial acetic acid and mixed well to dissolve completely. To this, was added salicylaldehyde (0.02mol) and fused sodium acetate (1.8g). The completion of reaction was controlled by TLC analysis, and completed in about 45min. The content was then poured in about 1000ml of cold water, the yellow precipitate was separated out, filtered and washed with cold water, dried and recrystallised from glacial acetic acid. Yield – 72%; m.p. -236°C; IR Data- 1694(C=O), 1185(C=S), 1249(C-N), 3170(N-H), 3414(O-H), 1522(C=C), 2910(C-H).

General procedure for synthesis of chloroacetamides⁸ (c₁₋₄)

Aromatic amines (0.01mol) were dissolved

Table 1: Characterization data of synthesized compounds c₁₋₄

Compd.	Yield (%)	m.p (°C)	R _f	IR data
c ₁	76	116	0.57	Ar.C-H 3076, Ali.C-H 2834, -CONH 1669-NH3264, C-N1395, Ar.C=C 1511.
c ₂	60	73	0.56	—
c ₃	70	126	0.72	—
c ₄	53	150	0.45	Ar.C-H 3010, Ali.C-H 2838, -CONH 1667 NH 3295, C-N 1345, Ar. C=C 1512, -OCH ₃ 1022.

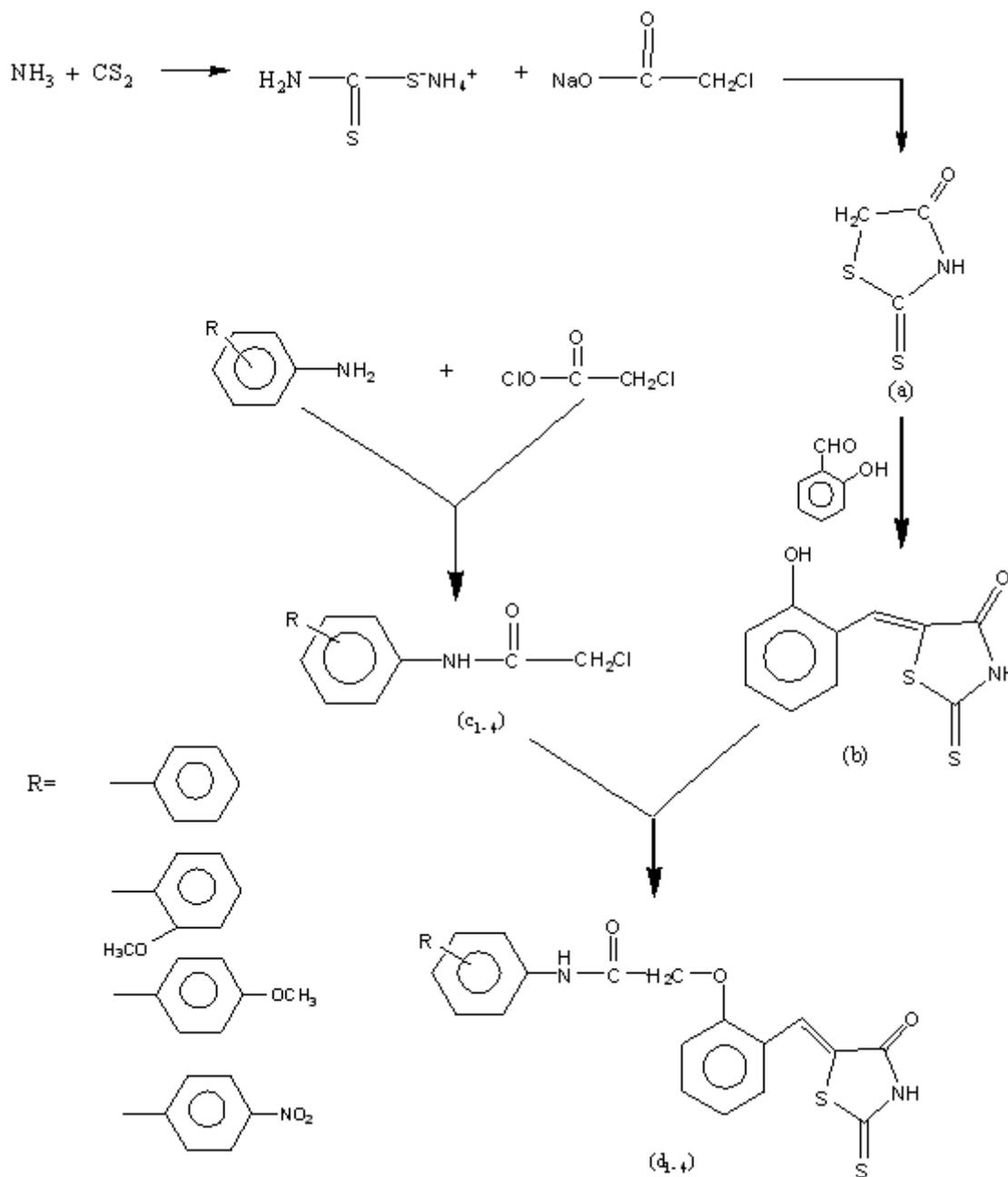
Table 2: Characterization data of synthesized compounds d₁₋₄

Compd.	yield (%)	m.p (°C)	R _f	¹ H NMR data
d ₁	48	256	0.14	Ar-H(m,6.94-7.66), -NHCO- (s,10.01), ring-NH- (s,13.4), -CH=(s,8.07)
d ₂	52	248	0.12	Ar-H(m,6.94-7.86), -NHCO- (s,9.99), ring-NH- (s,12.8), -CH=(s,8.01), -OCH ₃ (s,3.86)
d ₃	42	278	0.16	Ar-H(m,6.94-7.62), -NHCO- (s,10.03), ring-NH- (s,13.2), -CH=(s,7.98), -OCH ₃ (s,4.01)
d ₄	44	284	0.13	Ar-H(m,6.96-7.82), -NHCO- (s,9.81), ring-NH- (s,12.9), -CH=(s,8.03)

in 10ml of glacial acetic acid containing 50ml of saturated solution of sodium acetate. The solution was cooled in an ice bath and chloroacetyl chloride (0.01mol) was added dropwise to the mixture. The white precipitate separated was filtered, washed with 50% acetic acid and recrystallised from ethanol Table 1.

General procedure for synthesis of d_{1-4} ^{7,8}

The compounds c_{1-4} (0.01mol) were dissolved in ethanol (10ml), triethylamine (0.01mol) was added to the solution. To this reaction mixture 0.01mol of (b) was added. The reaction mixture was refluxed and completion of reaction was controlled



by TLC analysis, usually completed in about 18-20 hrs. Cooled the reaction mixture, added ice pieces to it and little distilled water, then the product was extracted with ethyl acetate twice, 25ml each time. The ethyl acetate was removed under vacuum to provide crude d_{1-4} which then recrystallised from ethanol Table 2.

***In-vivo* study**

Acute toxicity study

All the compounds were screened for acute oral toxicity study according to OECD guidelines⁹. The compounds synthesized d_{1-4} were found to have LD_{50} in range 500-600mg/kg b.w. in female mice.

Anti-convulsant studies

The compound d_{1-4} were screened for their anti-convulsant activity against electroshock-induced convulsion in mice of either sex (weighing 20-30g) by the method given in literature¹⁰. The compounds were suspended in 5% gum acacia solution and injected i.p. at a dose of 50mg/kg b.w. After 1hr. the animals subjected to a current of 60mA/50Hz for 0.2sec. and the effect was observed. Compounds d_{-1} , d_{-2} , d_{-3} and d_{-4} provided 95,70,60 and

85% protection respectively against the electroshock-induced convulsion in mice compared to 100% activity of phenytoin (a reference drug) at a dose of 25mg/kg b.w.

RESULTS AND DISCUSSION

In present study the compounds d_{1-4} were synthesized and their physical and spectral analysis was done. Their purity was checked by TLC that gave satisfactory results. The compounds synthesized reflects remarkable anti-convulsant activity by MES method at a lower dose i.e. 50mg/kg b.w. The compounds showed lower toxicity than parent compound (b).

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