Asian Journal of Chemistry Vol. 18, No. 1 (2006), 155–158

Synthesis of Hydantoin, Thiohydantoin and Desulphuration of Thiohydantoin to Hydantoin†

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Condensation of benzil (or α-diketone obtained from auroneepoxide) with urea, thiourea and substituted thiourea in presence of ethanol in alkaline medium leads to the formation of hydantoin, thiohydantoin and substituted thiohydantoin. All the compounds were purified and analyzed using physical and chemical methods and were further confirmed by spectral studies. The antimicrobial effect was studied by using cup-plate (nutrient-agar) technique on six different pathogenic microorganisms. The synthesised compounds were screened for their anti-AIDS property.

Key Words: Synthesis, Hydantoin, Thiohydantoin, Desulphuration.

INTRODUCTION

Earlier workers have reported the preparation of 2-thiohydantoin and their various applications in the field of medicine. Thiones and nitrones reactions are also reported[1] in the field of medicine. Benzil (α-diketone) reacts under alkaline conditions in ethanolic medium with 1,3-dimethyl-4,5-diphenyl tetrahydro imidazone-2-thione, 3-methyl-5,5-diphenyl-2-thiohydantoin and -5,5-diphenyl-thiohydantoin respectively[2]. In continuation of the reported 2-thiohydantoin synthesis, it was thought interesting to take up synthesis of thiohydantoin and substituted thiohydantoins.

EXPERIMENTAL

All the melting points are uncorrect. The IR-spectra are recorded on Perkin-Elmer 983 spectrophotometer and PMR on Brucker AC 300F.

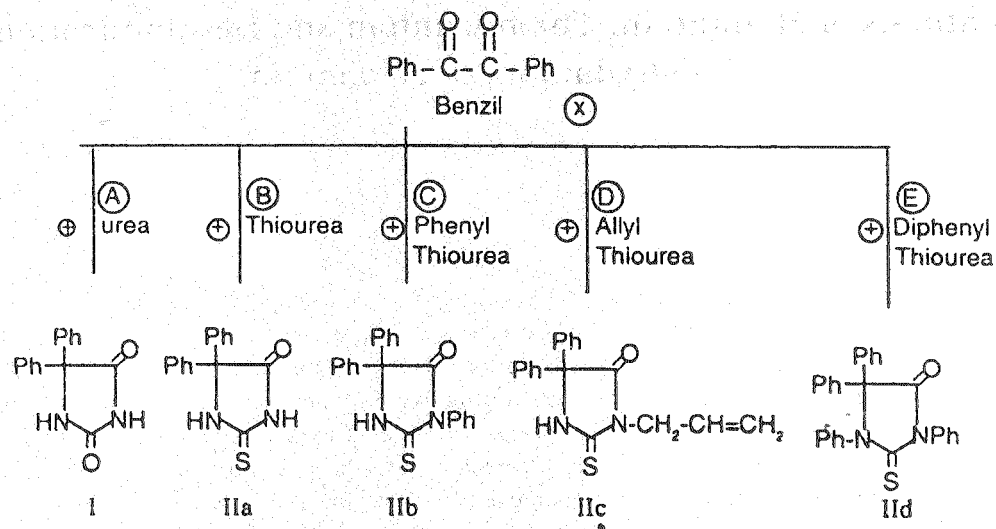
(i) Preparation of 5,5-diphenyl hydantoin (I), 5,5-diphenyl-2-thiohydontoin and its substituted derivatives (IIa–d)

A mixture of A or B or C or D or E (0.01 mol) **(Scheme-1)** dissolved in ethanol (20 mL), NaOH (0.2 g) and X was refluxed in a round bottom flask for 2.5 h. It was cooled, separated in acidified (dil. HCl) ice-cold water, filtered, washed with $NaHCO_3$ and water, dried and further recrystallized from ethanol-acetic acid mixture.

(I) UV: λ_{max} 217–275 nm for π-π* and n-π*. **(IIa)** UV: λ_{max} 208–275 nm for π-π* and n-π*.

As the above compounds I and II are known, the additional spectra were not taken.

†Part of this paper was presented in the 13th International Congress on Heterocyclic Chemistry held at Oregon State University, Corvallis, USA in the year 1991.



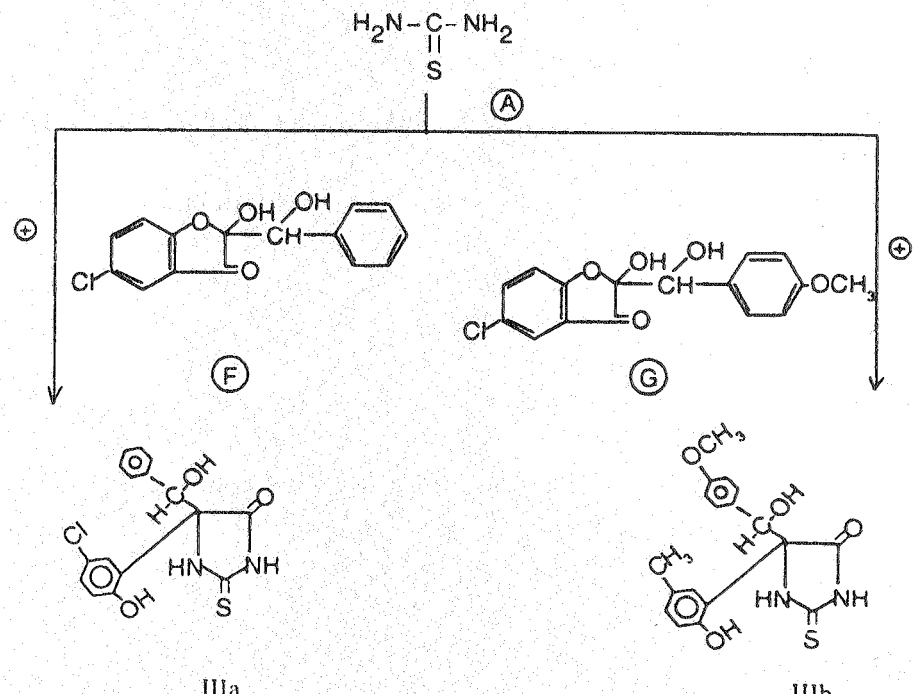
Scheme-1

(IIb) PMR: (δ) 5.9 (m). 15-H: (Ar-H), 9.8 (S). 1H (N—H). **(IIc)** UV: λ_{max} 210–276 nm for π-π* and n-π*. PMR: (δ) 3.6 (d) 2H (—CH_2—), 4.3 (d) 2H (=CH_2), 4.5 to 4.8 (m) 1H (—CH=), 5.9 (m) 10H (Ar-H) 9.8 (S) 1H (—N—H), Mass-spectra: m.w. 308, m.f. $C_{18}H_{17}N_2SO$.

(IId) In analogy with the other compounds it was considered to be 1,3,5,5-tetraphenyl-2-thiohydantoin.

(ii) Preparation of 5-(phenyl, hydroxy)-methyl-5-(2-hydroxy-5-chloro)-phenyl-2-thiohydantoin (IIIa) and 5-(4-methoxy-phenyl-hydroxy)-methyl-5 (2-hydroxy-5-methyl)-phenyl-2-thiohydantoin (IIIb)

A mixture of F or G (0.01 mol) with B (0.76 gm) **(Scheme-2)** was dissolved in ethanol (20 mL). NaOH (0.2 g) and refluxed for 2.5 h. It was prepared in identical conditions to get light-brown crystals of **(IIIa)** or **(IIIb)**, respectively.



Scheme-2

Desulphuration of Thiohydantoin

5,5-diphenyl-2-thiohydantioin is subjected to desulphuration by using mercuric acetate and acetic acid. It was found to be identical with authentic sample of 5,5-diphenyl hydantoin (I) m.p. 2960C. No test for sulphur observed.

RESULTS AND DISCUSSION

The condensation of benzil[3] with urea, thiourea, phenyl thiourea, allyl thiourea, sym. diphenyl thiourea in alkaline medium and in presence of ethonol gave 5,5-diphenyl hydantoin **(I)**, 5-5-diphenyl-2-thiohydantain **(IIa)**, 3,5,5-triphenyl-2-thiohydantion **(IIb)**, 3-alkyl-5,5-diphenyl-2-thiohydantoin **(IIc)** and 1,3,5,5-tetraphenyl-2-thiohydantoin **(IId)**. Similarly, 5-chloro auro dihydroxide[4] and 5-methyl-4′-methoxy aurone dihydroxide on condensation with thiourea in alkaline medium and in presence of ethanol gave: 5(phenyl-hydroxy) methyl-5- (2-hydroxy-5-chloro) phenyl-2-thiohydantoin **(IIIa)** and 5-(4-methoxy-phenyl-hydroxy) methyl-5-(2-hydroxy-5-methyl) phenyl-2-thiohydantoin **(IIIb)**. The compounds thus synthesized in the series **(IIa–d)** described below are tested for their antimicrobial activities by cup-plate (N-agar) technique using DMSO as solvent against *P. vulgaris, E. coli, S. typhimurium, K. pneumonias, S. aureus* and *P. aeruginosa* at wells of 10 mm cut on the lawn culture on nutrient-agar plate. A control (DMSO without sample) was also studied against the above mentioned cultures (Table-1). Physical data and yield (%) of the compounds are presented in Table-2.

TABLE-1
ANTIMICROBIAL ACTIVITIES OF 2-THIOHYDANTOIN AND SUBSTITUTED 2-THIOHYDANTOIN

S. No.	Compound	*P. vulgaris*	*E. coli*	*S. typhimurium*	*K. pneumonias*	*S. aureus*	*P. aeruginosa*
1.	IIa	nil	nil	nil	1.1	1.2	nil
2.	IIb	nil	nil	1.3	nil	nil	nil
3.	IIc	nil	nil	nil	nil	1.2	1.4
4.	IId	nil	nil	1.1	nil	nil	1.3
5.	IIIa	nil	nil	1.4	1.1	nil	1.4
6.	IIIb	nil	nil	1.1	1.2	nil	1.1

(nil = no inhibition)

TABLE-2
MELTING POINT AND YIELD (PERCENTAGE) OF SYNTHESIZED COMPOUNDS*

S. No.	Compound	m.p. (°C)	Yield (%)
1.	I	296	75
2.	IIa	211	70
3.	IIb	250	70
4.	IIc	119	< 30
5.	IId	152	70
6.	IIIa	182	60
7.	IIIb	189	65

*C and H calculated and obtained are in good agreement.

Compound IIc has also been screened for its anti-AIDS activities at National Cancer Institute, Bethesda, Maeryland, USA (reported inactive).

ACKNOWLEDGEMENTS

The author expresses sincere thanks to Prof. (Dr.) B.J. Ghiya, Ex-Emeritus Professor, Organic Chem., Institute of Science, Nagpur for his help and guidance; Principal, Hislop College, Nagpur and Director, NEERI for antimicrobial activities and Dr. H.M. Meshram, Scientist, IICT, Hyderabad for spectral analysis.

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(*Reccived*: 11 December 2004; *Accpeted*: 5 Septenber 2005) AJC-4377