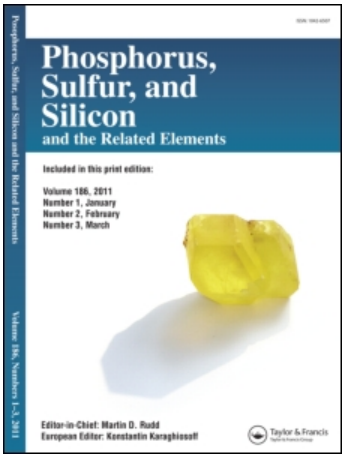

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REACTIONS WITH 2-THIOHYDANTOIN DERIVATIVES: SYNTHESIS OF MANNICH BASES AND IMIDAZOTHIAZOLE DERIVATIVES

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5-Arylidene-2-thiohydantoins (**1a–c**) and 5-arylazo-1-phenyl-2-thiohydantoins (**7a, b**) were condensed with formaldehyde and primary or secondary aromatic amines to give the corresponding Mannich bases (**2a–f**) and (**8a, b**) respectively, which could also be converted into the educts (**1a–c**) and (**7a, b**) by boiling in ethanolic HCl. On treatment of (**2a–f**), (**5a–c**) and (**8a, b**) with an ethereal diazomethane the colourless cyclopropane products (**3a–c**) and yellow N-methyl substituted compounds (**9a, b**) were isolated respectively. Alkylation of (**2d–f**) with methyl iodide and (**1a–c**) with 3-chloropentane-2,4-dione gave the corresponding 2-alkylmercapto derivatives (**5a–c**) and (**12a–c**) respectively, the former of which on hydrolysis by boiling ethanolic HCl afforded the hydantoin derivatives (**6a–c**). Cyclization of (**12a–c**) using polyphosphoric acid resulted in the formation of imidazothiazole derivatives (**13a–c**). The structure of the isolated products were established by elemental analyses and spectral data studies.

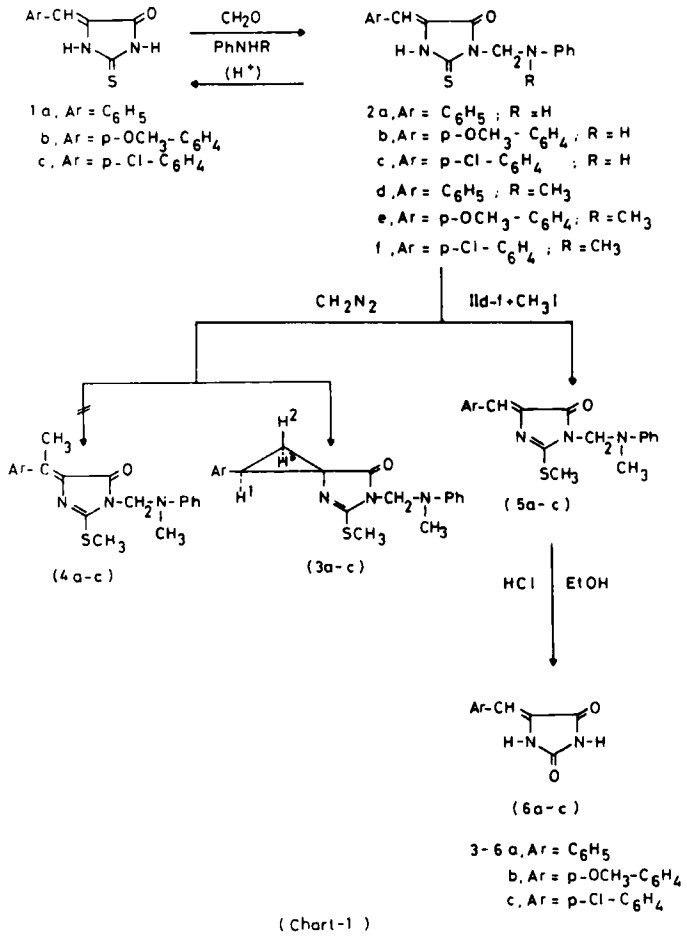
INTRODUCTION

The reported pharmacological activity[1,2] of Mannich bases of 2-thio-hydantoin derivatives stimulated our interest to continue our effort to synthesise additional new members of these derivatives. The present work was extended to the utility of alkylation of the readily obtainable 5-arylidene-2-thiohydantoins for the synthesis of new imidazothiazoles of potential biological activity.

RESULTS AND DISCUSSION

In conjunction with our previous report[3] on the synthesis of the Mannich bases (**2a, b**) via the reaction of 5-arylidene-2-thiohydantoins with primary aromatic amines and with formaldehyde, this paper will be concerned with the study of alkylation of the Mannich bases using diazomethane and/or alkyl halide as well as the synthesis of Mannich bases using secondary aromatic amines. It has been found that (**2a–c**) reacted with diazomethane to give colourless products containing three methylene groups more than the educts in each case. Structures (**3a–c**) or (**4a–c**) could, however, be considered for the reaction products (cf. Chart 1). S-Methylation and NHPh methylation were confirmed in the two possible structures as follow:

(1) The 5-arylidene-2-thiohydantoins (**1a–c**) reacted with formaldehyde and N-methylaniline in ethanol to yield the Mannich bases (**2d–f**). It has to be noted



(Chart-1)

here that the Mannich reactions were reported[3] previously to take place at position-3. Compounds (**2d–f**) regenerated (**1a–c**) when refluxed with conc. hydrochloric acid.

(2) When (**2d–f**) were treated with methyl iodide in ethanolic sodium ethoxide at room temperature 2-methylmercapto derivatives (**5a–c**) were obtained. Compounds (**5a–c**) gave correct analytical data. Moreover, when boiled their ethanolic solutions with conc. hydrochloric acid compounds (**5a–c**) afforded the 5-arylidene hydantoins (**6a–c**).[4]

(3) Compounds (**2d–f**) and/or (**5a–c**) and diazomethane under the same conditions gave the same products obtained by direct methylation of (**2a–c**) with diazomethane (melting points and mixed melting points determinations).

Structure (**4**) was readily ruled out on the basis of UV, IR and ^{1}H-NMR spectral data and structure (3) was, in turn, considered to represent the reaction products according to the following facts:

(a) The UV absorption spectrum of (**2a**) eg. showed a maximum at 358 mμ. This absorption maximum is compatible with a benzene ring conjugated with a

C=C bond which is, in turn conjugated with a C=O group. The very significant band at 358 mμ is entirely absent in the spectrum of (**3a**), this reveals that the conjugation has been interrupted.

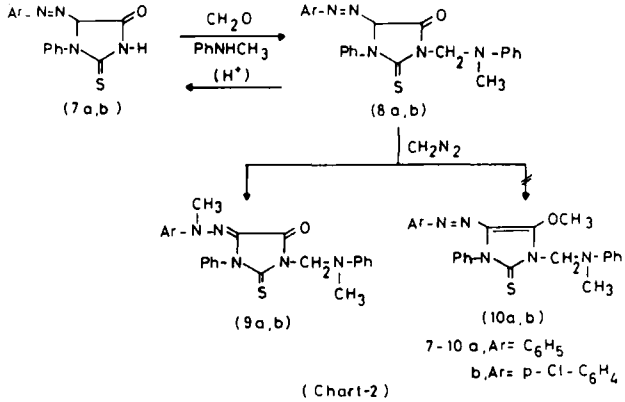
(b) The IR spectrum of (**3a**) e.g. exhibited strong absorption bands for the C=O and C=N groups at 1710 and 1640 cm^{-1} respectively and showed also the absence of NH absorption bands.

(c) The ^{1}H-NMR spectrum (**3a**) revealed an ABX pattern similar to that reported for cyclopropane derivatives.[5] E.g., the spectrum revealed the presence of three double doublet signals centered at δ 2.2, 2.5, 2.7. However, not all the expected 12 lines were observed due to the overlap of some of the outer lines of the splitted signals.[6] The assignment of the chemical shifts of the three protons H_1, H_2 and H_3 was based on the values of the coupling constants[7] namely $J_{1,3} = 8$ Hz, $J_{1,2} = 6$ Hz and $J_{2,3} = 5$ Hz. The ^{1}H NMR (ppm) spectrum of (**3a**) revealed also signals at 3.1 (s, 3H, N—CH_3); 2.7 (s, 3H, S—CH_3); 4.1 (s, 2H, N—CH_2—N) and 7.2–7.5 (m, 10H, aromatic protons). These assignments were based in comparison with the chemical shifts of ^{1}H-NMR spectrum of (**5a**).

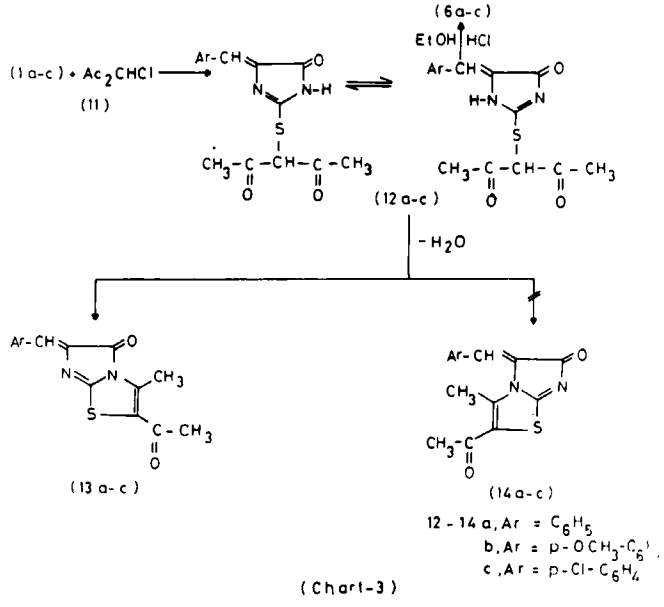
When the 5-arylazo-1-phenyl-2-thiohydantoin derivatives (**7a, b**) were treated with formaldehyde and N-methylaniline the hydrogen atom of the imino group at position-3 is sufficiently active to take part in a Mannich reaction and to give high yields of 3-N-methylanilinomethyl-2-thiohydantoin derivatives (**8a, b**), which regenerated (**7a, b**) when refluxed with hydrochloric acid. The structures of the yellow Mannich bases were inferred from both elemental analyses and spectral data studies (cf. Experimental Part).

Treatment each of (**8a, b**) with an ethereal solution of diazomethane, afforded only one isolable product which could be formulated as (**9a, b**) or (**10a, b**) (cf. Chart 2). Moreover, the IR spectra of the reaction products showed a strong carbonyl (C=O) as well as a (C=N) absorption, therefore, structure (**10a, b**) was ruled out and (**9a,b**) were the only isolable products.

The present work was extended to investigate the possibility of alkylating the readily obtainable 5-arylidene-2-thiohydantoins (**1a–c**) in order to synthesise of new imidazothiazoles of potential biological activity. Thus, it has been found that



(Chart-2)



(Chart-3)

3-chloropentane-2,4-dione (**11**) reacted with 5-arylidene-2-thiohydantoins (**1a–c**) in ethanolic sodium ethoxide at room temperature to give products corresponding to the addition of one molecule of the ylidene to one molecule of the dione followed by the loss of one molecule of HCl. The reaction products were thus assigned structure (**12a–c**) on the basis of elemental analyses and spectral data. The IR spectra of the reaction products revealed an absorption band characteristic for the presence of a ring C=O group in each case. This proves that the ring carbonyl group in the thiohydantoin derivatives (**1a–c**) did not take part in the condensation reaction leading to the formation of (**12a–c**). Compounds (**12a–c**) could be hydrolysed by boiling their ethanolic solutions with conc. hydrochloric acid to give back the hydantoin derivatives (**6a–c**)[4] respectively. Cyclisation of (**12a–c**) using polyphosphoric acid afforded products which could be formulated as the imidazothiazoles (**13a–c**) or (**14a–c**) respectively based on both elemental analyses and spectral data studies (cf. Experimental Part).

Structure (**13a–c**) was considered more probably to represent the cyclisation products on the basis that the hydrogen atom attached to the nitrogen atom in position-3 facilitates the loss of H_2O which is necessary for completion of the cyclisation step. This fact was supported by the reports that N–3 position is the only active site in the 5-arylidene-2-alkylmercapto hydantoins.[3,8] Moreover, this finds parallelism from our previous work[9] on reaction of anthranilic acid with 5-arylidene-2-methylmercapto hydantoins to give 2-arylideneimidazo[2,1-b]-quinazoline-3,5-diones.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP 3-300 spectrophotometer in KBr discs. The ^{1}H-NMR spectra were recorded on a Varian EM 490–90 MHz

spectrometer in deuterated DMSO-d_6 as a solvent and TMS as internal standard, chemical shifts are expressed as δ [ppm units]. Microanalytical data were performed by the Microanalytical Center at the Faculty of Science, Cairo University.

Mannich bases of 5-arylidene-2-thiohydantoins (**1a–c**) *and 5-arylazo-1-phenyl-2-thiohydantoins* (**7a, b**)
General procedure: To a suspension of each of (**1a–c**) and (**7a–b**) (0.01 mole), the appropriate amine (0.011 mole) in ethyl alcohol (50 ml) was added 30% aqueous formaldehyde (1.1 ml). The reaction mixture was refluxed on a water bath for 2 hours. The solid product obtained on cooling was crystallised from ethyl alcohol as yellow crystals of (**2c–f**) and (**8a, b**) respectively (cf. Table 1 and 2).

Action of concentrated hydrochloric acid on (**2c–f**), (**8a, b**), (**5a–c**) *and* (**12a–c**)
General procedure: A suspension of each of **2c–f, 8a, b, 5a–c** and **12a–c** (1 g) in a mixture of conc. hydrochloric acid (8 ml) and ethanol (20 ml) was heated under reflux for 2 hours. The reaction

TABLE I

Characterization data of compounds **2c–f**; **3a–c**; **5a–c**; **8a, b**; **9a, b**; **12a–c** and **13a–c**

Compound	M.P. (°C)	Yield (%)	Mol. formula	% Analysis Calcd./Found C	H	N	S	Cl
2c	150	88	$C_{17}H_{14}N_3OSCl$	59.38	4.07	12.22	9.31	10.33
				59.5	4.3	12.0	9.5	10.6
2d	165	85	$C_{18}H_{17}N_3OS$	66.87	5.26	13.00	9.9	—
				66.6	5.5	12.8	10.1	—
2e	180	86	$C_{19}H_{19}N_3O_2S$	64.58	5.38	11.89	9.06	—
				64.7	5.2	11.7	9.1	
2f	210–2	83	$C_{18}H_{16}N_3OSCl$	60.41	4.47	11.74	8.95	9.93
				60.5	4.3	11.9	9.1	9.8
3a	120	75	$C_{20}H_{21}N_3OS$	68.37	5.98	11.96	9.11	—
				68.2	6.2	11.8	9.0	—
3b	133	77	$C_{21}H_{23}N_3O_2S$	66.14	6.03	11.02	8.39	—
				66.4	5.8	10.8	8.6	—
3c	170	70	$C_{20}H_{20}N_3OSCl$	62.25	5.18	10.89	8.30	9.20
				62.1	5.4	10.6	8.5	9.0
5a	138–9	80	$C_{19}H_{19}N_3OS$	67.65	5.63	12.46	9.49	—
				67.8	5.9	12.6	9.3	—
5b	145	82	$C_{20}H_{21}N_3O_2S$	65.39	5.72	11.44	8.71	—
				65.5	5.4	11.6	8.5	—
5c	185–6	78	$C_{19}H_{18}N_3OSCl$	61.37	4.84	11.30	8.61	9.55
				61.5	5.0	11.1	8.5	9.7
8a	140	80	$C_{23}H_{21}N_5OS$	66.50	5.06	16.86	7.71	—
				66.3	5.2	16.6	7.9	—
8b	181–2	77	$C_{23}H_{20}N_5OSCl$	61.40	4.44	15.57	7.11	7.89
				61.5	4.6	15.7	7.0	7.6
9a	110–2	70	$C_{24}H_{23}N_5OS$	67.13	5.36	16.31	7.45	—
				67.5	5.1	16.2	7.3	—
9b	142	68	$C_{24}H_{22}N_5OSCl$	62.13	4.74	15.10	6.90	7.65
				62.0	4.5	15.3	7.0	7.8
12a	170	62	$C_{15}H_{14}N_2O_3S$	59.60	4.67	9.27	10.58	—
				59.8	4.9	9.4	10.7	—
12b	176	60	$C_{16}H_{16}N_2O_4S$	57.83	4.85	8.43	9.63	—
				57.6	5.0	8.2	9.8	—
12c	193	65	$C_{15}H_{13}N_2O_3SCl$	53.49	3.85	8.32	9.51	10.54
				53.7	4.0	8.5	9.6	10.7
13a	163	70	$C_{15}H_{12}N_2O_2S$	63.38	4.26	9.86	11.25	—
				63.5	4.5	10.0	11.0	—
13b	174–5	68	$C_{16}H_{14}N_2O_3S$	61.14	4.49	8.91	10.18	—
				61.3	4.2	9.1	10.3	—
13c	200–2	65	$C_{15}H_{11}N_2O_2SCl$	56.52	3.45	8.79	10.05	11.15
				56.2	3.7	8.5	9.9	11.0

TABLE II

Spectral data of compounds **2c, d, f**; **3b**; **5a, c**; **8a, b**; **9a, b**; **12a–c** and **13a–c**

Compound	IR [cm^{-1}]	^{1}H-NMR [δ ppm]
2c	3370, 3340 (2NH); 2980 (CH_2); 1710 (C=O) and 1200 (C=S).	
2d	3350 (NH); 1710 (C=O) and 1200 (C=S).	2.9 (s, 3H, N—CH_3); 4.0 (s, 2H, N—CH_2—N); 6.8 (s, 1H, Ar—CH=); 7.2–7.5 (m, 10H, Ar—H) and 9.8 (s, 1H, NH disappeared after D_2O exchange).
2f	3370 (NH); 1720 (C=O) and 1205 (C=S).	
3b	1720 (C=O) and 1640 (C=N).	
5a	1710 (C=O) and 1630 (C=N).	2.7 (s, 3H, S—CH_3); 3.0 (s, 3H, N—CH_3); 4.0 (s, 2H, N—CH_2—N); 6.8 (s, 1H, Ar—CH=) and 7.2–7.4 (m, 10H, ArH).
5c	1720 (C=O) and 1640 (C=N).	
8a	1720 (C=O) and 1200 (C=S).	
8b	1725 (C=O) and 1210 (C=S).	
9a	1710 (C=O); 1635 (C=N) and 1210 (C=S).	2.9, 3.0 (2s, 6H, 2N—CH_3); 4.0 (s, 2H, N—CH_2—N) and 7.2–7.6 (m, 15H, ArH).
9b	1720 (C=O), 1640 (C=N) and 1210 (C=S).	
12a	3380 (NH); 1720, 1700 (ring C=O and acetyl C=O) and 1640 (C=N).	2.1 (s, 6H, $2CH_3$); 4.2 (s, 1H, S—CH); 6.9 (s, 1H, Ar—CH=) and 7.1–7.4 (m, 5H, ArH) and 8.2 (s, 1H, NH exchangeable with D_2O).
12b	3400 (NH); 1725, 1700 (ring C=O and acetyl C=O) and 1630 (C=N).	
12c	3400 (NH); 1735, 1700 (ring C=O and acetyl C=O) and 1635 (C=N).	
13a	2900 (saturated CH); 1720, 1690 (2 C=O) and 1630 (C=N).	2.1, 2.3 (2s, 6H, $2CH_3$); 6.8 (s, 1H, Ar—CH=) and 7.2–7.4 (m, 5H, ArH).
13b	2930 (saturated CH); 1725, 1700 (2 C=O) and 1630 (C=N).	
13c	2920 (saturated CH); 1720, 1700 (2 C=O) and 1640 (C=N).	

mixture was allowed to cool and the obtained solid was collected by filtration and crystallised from acetic acid and identified the products as: **2c** give **1c**, **2d–f** give **1a–c**,[10] **8a, b** give **7a, b**,[11] **5a–c** and **12a–c** give **6a–c**,[4] by melting points and mixed melting points determinations.

Alkylation of **1a–c** *and* **2d–f**

General procedure: A solution of each of **1a–c** and **2d–f** (0.01 mole) in ethanol (40 ml) containing sodium ethoxide (prepared from 0.25 g, 0.011 g atom sodium) were treated with 3-chloropentane-2,4-dione and methyl iodide respectively (0.01 mole). The reaction mixture was stirred for 2 hours and left overnight at room temperature and the solid so obtained was filtered off, washed with water and then crystallised from ethanol to give pale yellow crystals of **12a–c** and **5a–c** respectively (cf. Tables 1 and 2).

Action of ethereal diazomethane on **2a–f, 5a–c** *and* **8a, b**

General procedure: An ethereal diazomethane solution (from 4 g of nitrosomethylurea) was added to 1 gm of each of **2a–f, 5a–c** and **8a, b** suspended in 50 ml of ether, and in the presence of two drops of methanol. The reaction mixture was kept overnight in the ice box and then treated with a fresh amount of an ethereal diazomethane solution (from 4 g nitrosomethylurea). After three days, the reaction mixture was evaporated and the solid, so obtained, from the action of diazomethane on each of **2a–c, 2d–f** and **5a–c** was crystallised from ethanol as a colourless crystals. The products were identified as **3a–c** by melting point and mixed melting point determinations. The solid, so obtained, from the action of diazomethane on **8a, b** were crystallised from ethanol as yellow crystals of **9a, b** (cf. Tables 1 and 2).

Action of polyphosphoric acid on **12a–c**

A mixture of each of 1 g of **12a–c** and polyphosphoric acid (prepared from 4 g of phosphorus pentoxide and 3 ml of 85% phosphoric acid) was heated on the water-bath for 1 hour, then in an oil-bath (125–130°C) for 30 minutes. After cooling, the reaction mixture was poured onto ice-cold water and neutralised with potassium carbonate solution. The solid thus obtained was crystallised from ethanol to give brown crystals identified as **13a–c** (cf. Tables 1 and 2).

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