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Synthesis, Antibacterial and Antifungal Activity of Some New Thiohydantoin Derivatives

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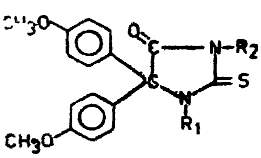
Some new methoxy aryl substituted-2-thiohydantions and their mercurated derivatives have been synthesised. Both mercurated and non-mercurated compounds have been screened for antibacterial activity against *S. aureus* and *E. coli* and for antifungal activity against *P. oryzae* (Cav.) *in vitro*.

A number of thiohydantoin derivatives are physiologically active and some of them have been reported to possess anticonvulsant[1], antibacterial[2], antifungal[3], antihypertensive[4] and such other properties. Encouraged by the findings and in continuation of our earlier work[5] 5,5-di-(*p*-methoxyphenyl)-3-aryl-2-thiohydantoins (I) and 5,5-di-(*p*-methoxyphenyl)-1,3-diaryl-2-thiohydantoins (II) have been synthesised by condensing anisil with various monoaryl and sym-diaryl thioureas respectively in presence of sodium ethoxide and anhydrous sodium acetate in absolute ethanol with a view to study their antibacterial and antifungal activity.



(I) R_1 = H, R_2 = Substituted aryl

(II) R_1 and R_2 = Substituted aryl.

The position of the phenyl nucleus at position-3 in case of thiohydantoin has been established by an unambiguous synthesis[5].

Further, monoacetoxy mercuric derivatives and diacetoxy mercuric derivatives are formed when both these thiohydantoins are mercurated with one or two equivalents of mercuric acetate respectively. The acetoxy mercuric group enters the *p*-position of the phenyl nucleus attached to the N-atom at position-3 of the monoacetoxy derivatives and 1- and 3-positions of the diacetoxy derivatives. The position of the acetoxy mercuric group in both cases have also been experimentally established[5].

Experimental

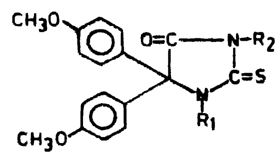
All melting points recorded are uncorrected. IR spectra (ν_{max} in cm^{-1}.) were recorded on KBr pellets. The $-N-C{=}S$ group frequency was obtained at 1270 cm^{-1} in case of 3-aryl-2-thiohydantoins and 1440 cm^{-1} in case of 1,3-diaryl-2-thioxyhydantoins.

TLC was carried out on silica gel-G layers of 250 μ thickness visualised by spraying Feigl's sodium azide-iodine reagent and the colourless spots were developed on a bluish back ground.

Anisil: It was prepared from anisaldehyde by the method used for the preparation of benzil[6].

*5,5-Di-(*p*-methoxyphenyl)-3-phenyl-2-thiohydantoin(I)*: In a clean dry conical flask (500 ml), metallic sodium (1g) was dissolved in well dried ethanol (120 ml). Monophenyl thiourea (1.52 g) and anisil (5.14 g) were added to this and the mixture was refluxed on a water bath for 8 hrs. The excess of alcohol was distilled off and a solution of sodium acetate (10 g in 400 ml water) was added to the residue. The whole was allowed to

TABLE 1—PHYSICAL CONSTANT OF 2-THIOHYDANTOINS



Sl. No.	R_1	R_2	Yield (%)	m.p. °C
1.	H	C_6H_5	70	170
2.	H	(*o*)-Cl C_6H_4	75	>250
3.	H	(*m*)-Cl.C_6H_4	75	>250
4.	H	(*p*)-Cl.C_6H_4	70	205
5.	H	(*o*)-CH_3.C_6H_4	65	210
6.	H	(*m*)-CH_3.C_6H_4	75	180
7.	H	(*p*) CH_3.C_6H_4	65	195
8.	H	(*o*)-NO_2.C_6H_4	75	185
9.	H	(*m*)-NO_2.C_6H_4	75	>250
10.	H	(*p*)-NO_2.C_6H_4	60	>250
11.	H	(*o*)-COOH.C_6H_4	75	230
12.	H	(*p*)-COOH.C_6H_4	70	237
13.	H	(α)-$C_{10}H_7$	70	185
14.	C_6H_5	C_6H_5	75	180
15.	*o*-Cl.C_6H_4	*o*-Cl.C_6H_4-	70	177
16.	*m*-Cl.C_6H_4	*m*-Cl.C_6H_4-	75	185
17.	*p*-Cl.C_6H_4	*p*-Cl.C_6H_4-	65	>250
18.	*p*-Br.C_6H_4	*p*-Br.C_6H_4-	75	215
19.	*o*-CH_3.C_6H_4	*o*-CH_3.C_6H_4-	75	>250
20.	*m*-CH_3.C_6H_4	*m*-CH_3 C_6H_4-	75	>250
21.	*p*-CH_3.C_6H_4	*p*-CH_3.C_6H_4-	65	>250
22.	*o*-NO_2.C_6H_4	*o*-NO_2.C_6H_4-	75	190
23.	*m*-NO_2.C_6H_4	*m*-NO_2.C_6H_4-	75	185
24.	*p*-NO_2.C_6H_4	*p*-NO_2.C_6H_4-	60	250
25.	*o*-COOH C_6H_4	*o*-COOH.C_6H_4-	75	>250
26.	*p*-COOH.C_6H_4	*p*-COOH.C_6H_4-	70	235
27.	(α)-$C_{10}H_7$-	(α)-$C_{10}H_7$-	75	>250

All the compounds exhibited consistent analyses for S.

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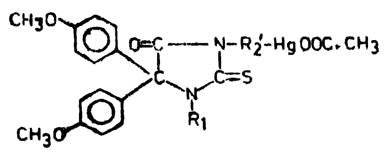
stand over night. On the next day, it was filtered at the pump. The filtrate was saturated with carbondioxide when (I) precipitated out. The precipitate was filtered off, washed several times with water and was dissolved in dilute sodium hydroxide solution. The precipitate reappeared on resaturating the solution with carbon dioxide. The precipitate thus obtained was finally crystallised from water : alcohol (1:1 v/v) mixture. m.p. 170° : Yield 70% : Found : S, 8.13%. $C_{23}H_{20}O_3N_2S$ requires S, 7.92%

The m.p., yield and analytical data of similarly prepared 5, 5-di-(*p*-methoxyphenyl)-3-aryl-2-thiohydantoins and 5,5-di-(*p*-methoxyphenyl)-1,3-diaryl-2-thiohydantoins are given in Table 1.

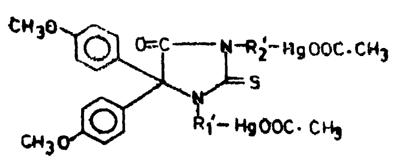
TABLE 2—PHYSICAL CONSTANT OF MONOACETOXYMERCURI DERIVATIVES OF 2-THIOHYDANTOINS



Sl. No.	R_1	R'_2	Yield (%)	m.p. °C
1.	H	C_6H_4-	75	>250
2.	H	*o*-Cl.C_6H_3-	70	250
3.	H	*m*-Cl.C_6H_3	75	>250
4.	H	*p*-Cl C_6H_3	70	>250
5.	H	*o*-CH_3.C_6H_3	70	250
6.	H	*m*-CH_3.C_6H_3	75	>250
7.	H	*p*-CH_3.C_6H_3	65	>250
8.	H	*o*-NO_2.C_6H_3	75	>250
9.	H	*m*-NO_2.C_6H_3	75	>250
10.	H	*p*-NO_2 C_6H_3	65	>250
11.	H	*o*-COOH.C_6H_3	70	>250
12.	H	*p*-COOH.C_6H_3	70	>250
13.	H	(α)-$C_{10}H_6$-	75	>250

All the compounds exhibited consistent analyses for Hg.

TABLE 3—PHYSICAL CONSTANT OF DI-ACETOXY MERCURI DERIVATIVES OF 2-THIOHYDANTOINS



Sl. No.	R'_1	R'_2	Yield	m.p. °C
1.	C_6H_4-	C_6H_4-	75	>250
2.	*o*-Cl.C_6H_3	*o*-Cl.C_6H_3-	70	>250
3.	*m*-Cl.C_6H_3	*m*-Cl.C_6H_3	70	235
4.	*p*-Cl.C_6H_3	*p*-Cl.C_6H_3	65	>250
5.	*p*-Br.C_6H_3	*p*-Br.C_6H_3	70	>250
6.	*o*-CH_3.C_6H_3	*o*-CH_3.C_6H_3	70	>250
7.	*m*-CH_3.C_6H_3	*m*-CH_3.C_6H_3	70	>250
8.	*p*-CH_3 C_6H_3	*p*-CH_3.C_6H_3	65	>250
9.	*o*-NO_2.C_6H_3	*o*-NO_2.C_6H_3	60	240
10.	*m*-NO_2.C_6H_3	*m*-NO_2.C_6H_3	60	>250
11.	*p*-NO_2.C_6H_3	*p*-NO_2.C_6H_3	60	230
12.	*o*-COOH.C_6H_3	*o*-COOH.C_6H_3	75	>250
13.	*p*-COOH.C_6H_3	*p*-COOH.C_6H_3	75	>250
14.	(α)-$C_{10}H_6$-	(α)-$C_{10}H_6$-	70	>250

All the compounds exhibited consistent analyses for Hg.

5,5-Di- (p-methoxyphenyl)- 3- (p-acetoxymercuri phenyl)-2-thiohydantoin(II) : 5, 5 - Di-(*p*-methoxyphenyl)-3-phenyl-2-thiohydantoin (1 g), dissolved in minimum volume of hot acetic acid was treated with a solution of mercuric acetate (1 g in minimum volume of 1:1 v/v alcohol and acetic acid). The mixture was stirred well and left over night at room temperature. The precipitate formed was filtered and washed repeatedly with slight warm water, dilute alcohol and finally very dilute acetic acid. m.p. >250° Yield 75% : Found : Hg, 30.31%, $C_{25}H_{22}N_2O_5SHg$ requires Hg, 30.27%.

The m.p., yield and analytical data of similarly prepared 5,5-di-(*p*-methoxy phenyl)-3-(acetoxy mercuri aryl)- and 5,5-di-(*p*-methoxy phenyl)-1,3-di-(acetoxymercuriaryl)-2-thiohydantoins are given in Table 2 and 3 respectvely.

Fungicidal activity : Both mercurated and non-mercurated compounds were screened for their antifungal activity against the test fungus *Piricularia oryzae* (Cav.) by the method of Montgomery and Moore[7] with a slight modification. The dilution in ppm of both mercurated and non-mercurated compounds for 50 per cent germination of the fungus was noted. From the analysis of fungicidal results, it was observed that these compounds in general are much less active due to the inactivating effect of the *p*–methoxy phenyl substituent at 5-position.

Antimicrobial screening : The antimicrobial screening of all the compounds was done by Rideal-Walker Serial Drop Dilution Method[8] against the two test bacteria *E. coli* and *S. aureus*. It was observed that all the compounds were inactive against both gram +ve and gram –ve bacteria.

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