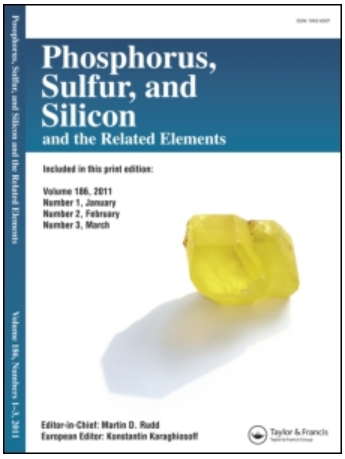

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CHLOROSULFONATION OF 5,5-DIPHENYLHYDANTOIN AND 5-ARYLIDENEBARBITURIC ACIDS

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CHLOROSULFONATION OF 5,5-DIPHENYLHYDANTOIN AND 5-ARYLIDENEBARBITURIC ACIDS

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5,5-Diphenylhydantoin (1) by heating with chlorosulfonic acid gave a bis-sulfonyl chloride (2) in which the orientation of sulfonation is apparently meta/para. The chloride (2) was converted into 8 sulfonamides (**3–10**). Barbituric acid has been condensed with aromatic aldehydes to yield 18 5-arylidene derivatives (11–28). The reaction of chlorosulfonic acid with 5-benzylidenebarbituric acid (11) is discussed together with the subsequent reaction of the sulfonyl chloride with amines. The chlorosulfonation of other arylidenebarbituric acids (12–14, 22, 23, 26 and 28) has also been examined.

Key words: 5,5-Diphenylhydantoin; 5-arylidenebarbituric acids; chlorosulfonation; sulfonamides; Michael addition.

The reaction of 5-benzylidenebarbituric acid sulfonyl chloride (29) with amines generally affords a mixture of the sulfonamide and the corresponding Michael addition product, in which the amine adds across the alkylidene double bond. With the more bulky, less reactive aniline only the benzylidene sulfonamide (35) was isolated. 5-(Benzylidene) (11)- and 5-(*p*-methoxybenzylidene) (14)- barbituric acids have been shown to add diethylamine and dimethylamine to give the adducts (37–39).

The work described in this paper is an extension of our previous studies[1–3] on the chemistry and biological properties of arylsulfonyl derivatives. 5,5-Diphenylhydantoin (phenytoin) has been extensively used as an anticonvulsant drug in the treatment of epilepsy[4]; the sulfonation of this compound has not been reported. It therefore appeared of interest to examine its reaction with chlorosulfonic acid, especially in view of the successful chlorosulfonation of many other compounds containing two phenyl rings.[1,2,5]

5,5-Diphenylhydantoin (1) did not react with excess of chlorosulfonic acid at room temperature (1 week) and at 100°C, TLC indicated the formation of base-line material which was water-soluble and was probably a sulfonic acid. However, (1), by reaction with boiling chlorosulfonic acid (12 mole equivalents), (4 hours) afforded the disulfonyl chloride (2, 82%). Repetition of the experiment under similar conditions, except that at the end of the reaction the mixture was treated with excess thionyl chloride at room temperature for 5 days afforded a slightly higher yield of (2) (88%) (Chart 1 and Table I). The mass spectrum did not show the molecular ion (M^+, 448) but did exhibit fragment ions at 415, 413 corresponding to M^+-Cl: the ratio of 9:6:1 for the intensities of the chlorine-containing ions was in agreement with a bis-sulfonyl chloride. The bis-sulfonyl chloride (2) was characterized by condensation with amines to give the sulfonamides (3–10 Chart 1 and

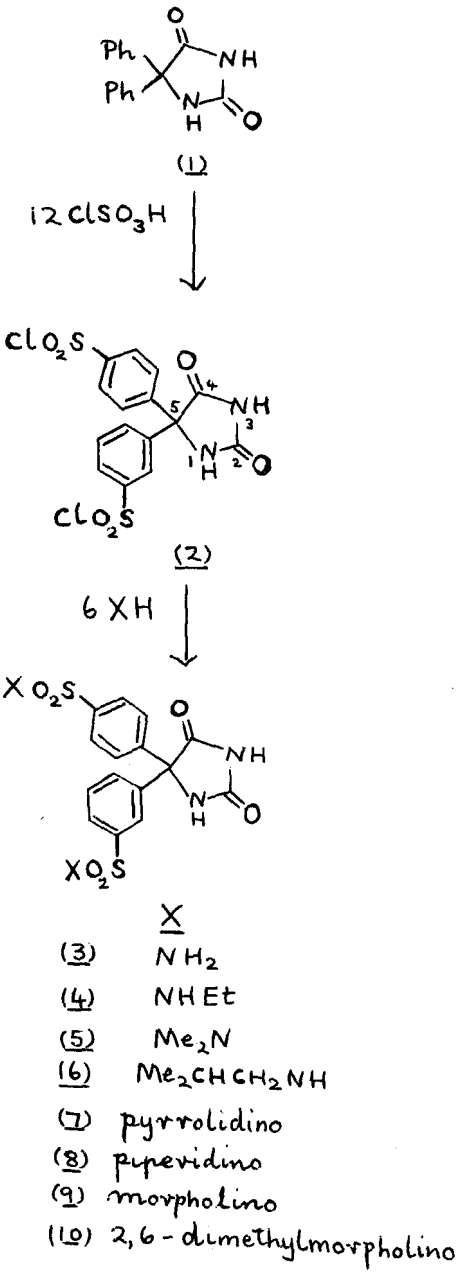


CHART 1 Derivatives of 5,5-diphenylhydantoin (**1**).

Table I) for biological evaluation. In contrast, attempted reaction of (2) with hydrazine, methylhydrazine and phenylhydrazine all failed to give isolatable products. The ^{1}H NMR spectrum of the dimethylsulfonamide (5) indicated that the multiplet due to the aromatic resonances (δ 7.85–7.50) had moved downfield, as

TABLE I

Physical data for the diphenylhydantoin sulfonyl derivatives

Comp. No	Yield (%)	m.p. (°C)	molecular formula	microanalysis found (calc.) % C	H	N	MS (M^+)
2	88	242-244	$C_{15}H_{10}Cl_2N_2O_6S_2$	39.9 (40.1)	2.4 (2.2)	6.0 (6.2)	415[a]
3	20	180	$C_{15}H_{14}N_4O_6S_2$	43.3 (43.9)	3.5 (3.4)	13.3 (13.6)	410
4	40	155	$C_{19}H_{22}N_4O_6S_2$	48.6 (48.9)	4.7 (4.7)	11.6 (12.0)	466
5	97	241-242	$C_{19}H_{22}N_4O_6S_2$	48.7 (48.9)	4.8 (4.7)	11.8 (12.0)	466
6	85	140-142	$C_{21}H_{26}N_4O_6S_2$	50.7 (51.0)	5.5 (5.3)	11.0 (11.3)	494
7	34	205	$C_{23}H_{26}N_4O_6S_2$	53.3 (53.3)	5.5 (5.8)	10.8 (10.8)	518
8	72	170	$C_{25}H_{30}N_4O_6S_2$	55.0 (54.9)	5.5 (5.5)	10.3 (10.2)	546
9	65	282-283	$C_{23}H_{26}N_4O_8S_2$	50.2 (50.2)	4.8 (4.7)	10.2 (10.2)	550
10	76	142-144	$C_{27}H_{34}N_4O_8S_2$	54.0 (53.5)	5.3 (5.6)	9.0 (9.2)	606

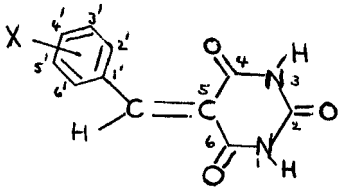
[a]=highest fragment ion corresponding to M^+-Cl

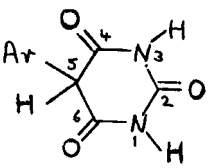
compared with diphenylhydantoin (1) (δ 7.4) due to greater deshielding by the sulfonyl groups. Study of the aromatic proton resonances shows the presence of an AA'BB' quartet indicating of *p*-sulfonation in one aromatic ring, but the overall pattern is complex implying a different orientation of substitution in the other phenyl ring. In view of the large size of the sulfonic acid group, *ortho*-sulfonation appears unlikely on steric grounds and it is therefore suggested that the second sulfonyl group is in the *m*-position as indicated in Chart 1. This hypothesis is supported by the two different methyl resonances (δ 2.6, 2.52), furthermore the ^{13}C-NMR spectrum showed 10 distinct aromatic carbon resonances whereas if 4,4'-disulphonation had occurred only 4 peaks would be expected.

The *m*,*p*-orientation of sulfonation of (1) is surprising, however previous workers[6] have reported a similar orientation for the major product from the nitration of (1). Mild nitration conditions were claimed to yield the *p*-mononitro derivative while further nitration, under more forcing conditions resulted, in the introduction of the second nitro group in the *m*-position.[6] This result may imply the operation of a long-range electronic effect, whereby the initially introduced *p*-nitro (or sulfonyl) moiety subsequently directs the second substituent into the *m*-position of the unsubstituted phenyl ring. Barbituric acid is known[7] to readily condense with aromatic aldehydes to form the corresponding 5-arylidene derivatives. The condensation occurs after a short period of heating and in the absence of base[8]; the reaction is much more facile than the analogous condensation with hydantoin, which requires prolonged heating with a base.[9] The difference is presumably a reflection of the lower electron density at the C_5-carbon atom in barbituric acid due to the presence of the two adjacent electron-withdrawing carbonyl groups.

In the present work, 18 arylidenebarbituric acids (11–28) have been obtained (Chart 2) as well-defined crystalline solids (Table II).

In previous studies,[11–13] we have demonstrated that benzylidene derivatives react smoothly with chlorosulfonic acid to yield the corresponding *para*-sulfonyl chlorides; in particular this applied to 5-benzylidenehydantoin.[9]





X	
(11)	H
(12)	2'-OMe
(13)	3'-OMe
(14)	4'-OMe
(15)	4'-F
(16)	2',3'-Cl_2
(17)	2',4'-Cl_2
(18)	3',4'-Cl_2
(19)	2',6'-Cl_2
(20)	2'-CF_3
(21)	4'-CF_3
(22)	4'-Ph

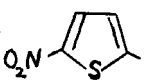
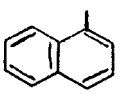
Ar	
(23)	PhCH=CH-
(24)	o-MeO.C_6H_4CH=CH-
(25)	PhCH=C(Me)-
(26)	
(27)	
(28)	

CHART 2 5-Arylidenebarbituric acids.

TABLE II

Physical data for the 5-arylidenebarbituric acids

Comp. No	Yield (%)	m.p. (°C)	Colour	molecular formula	microanalysis found (calc.) C	H	N	MS (M^+)
11	92	259-260 lit[9] 256	pale yellow	$C_{11}H_8N_2O_3$	60.9 (61.1)	3.7 (3.7)	12.9 (13.0)	216
12	94	276-277	pale yellow	$C_{12}H_{10}N_2O_4$	58.2 (58.5)	4.1 (4.1)	11.2 (11.4)	246
13	88	227-228	yellow	$C_{12}H_{10}N_2O_4$	58.4 (58.5)	3.9 (4.1)	11.6 (11.4)	246
14	93	297	yellow	$C_{12}H_{10}N_2O_4$	58.8 (58.5)	4.1 (4.1)	11.5 (11.4)	246
15	80	316-318	yellow	$C_{11}H_7FN_2O_3$	56.2 (56.4)	2.8 (3.0)	11.9 (12.0)	234
16	70	360-362	yellow	$C_{11}H_6Cl_2N_2O_3$	46.0 (46.3)	1.9 (2.1)	10.0 (9.8)	288*
17	85	345	yellow	$C_{11}H_6Cl_2N_2O_3$				288
18	78	275	yellow	$C_{11}H_6Cl_2N_2O_3$	46.5 (46.3)	2.0 (2.1)	9.9 (9.8)	288*
19	75	220	pale yellow	$C_{11}H_6Cl_2N_2O_3$	46.0 (46.3)	2.3 (2.1)	10.0 (9.8)	288*
20	40	215-217	yellow	$C_{12}H_7F_3N_2O_3$	50.5 (50.7)	2.7 (2.5)	10.0 (9.8)	284
21	82	275	cream	$C_{12}H_7F_3N_2O_3$	51.1 (50.7)	2.8 (2.5)	9.9 (9.8)	284
22	72	325-326	fawn	$C_{17}H_{12}N_2O_3$	70.4 (69.9)	4.3 (4.1)	9.8 (9.6)	292
23	82	268-270 lit[10] 270	yellow	$C_{13}H_{10}N_2O_3$	64.2 (64.5)	3.8 (4.1)	11.8 (11.6)	242
24	91	244-245	orange	$C_{14}H_{12}N_2O_4$	61.6 (61.8)	4.5 (4.4)	10.6 (10.3)	272
25	78	239	brown	$C_{14}H_{12}N_2O_3$	65.5 (65.6)	4.8 (4.7)	11.1 (10.9)	256
26	95	276	yellow	$C_9H_6N_2O_3S$	48.6 (48.6)	2.6 (2.7)	12.8 (12.6)	222
27	81	325	brown	$C_9H_5N_3O_5S$	40.0 (40.5)	1.7 (1.9)	15.3 (15.7)	267
28	97	280	bright yellow	$C_{15}H_{10}N_2O_3$	67.5 (67.7)	3.5 (3.8)	10.2 (10.5)	266

* Highest molecular mass of the ion cluster quoted.

By analogy, the chlorosulfonation of 5-benzylidenebarbituric acid (11) should provide a route to novel sulfonamido derivatives of 5-benzylidenebarbituric acid which have considerable potential biological activity, in view of the well-known pharmacological properties of many barbiturates as sedative-hypnotic and anti-convulsant drugs.[14]

Chlorosulfonation of 5-benzylidenebarbituric acid (11) would be expected to yield the corresponding *p*-sulfonyl chloride (cf. Reference 9). This would be the preferred orientation of sulfonation due to the powerful electron-donating property (+M effect) of the alkylidene double bond.

The reaction of (11) with chlorosulfonic acid was examined using 6 and 12 molar equivalents of the reagent for one week at room temperature. Treatment with ice

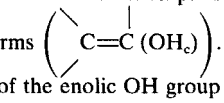
gave a product that could not be completely dried, because it decomposed in the vacuum desiccator (fumes of hydrogen chloride evolved) to a yellow syrup, which was soluble in water and was concluded to be the sulfonic acid. On the other hand, when the reaction was performed with a very large excess of chlorosulfonic acid (20 molar equivalents) the product was a yellow powder (85%, m.p. 125°C decomp.) which appeared to be reasonably stable. These conditions are similar to those used for the chlorosulfonation of 5-benzylidenehydantoin; the large excess of the reagent needed may be due to interaction with the NH groups of the barbituric acid.

The reaction of (11) was also studied using various quantities of chlorosulfonic acid (3 to 12 molar equivalents) in excess thionyl chloride giving products (54 to 67% yields) with melting points ranging from 138 to 210°C (decomp.) which varied with the rate of heating. The products are very difficult to obtain completely dry, traces of moisture also affect the melting points.

The optimum conditions for the chlorosulfonation of (11) appeared to involve treatment with a mixture of chlorosulfonic acid (6 molar equivalents) and excess thionyl chloride to give the sulfonyl chloride (29) (80%), m.p. 180° (decomp.) as this appeared to be the purest product. No suitable solvent system could be found for TLC analysis, however the ^{1}H NMR spectrum was in agreement with the assigned structure; in particular, the aromatic proton resonances (δ 8.0–7.6) showed a well-defined AA′BB′ pattern indicative of *p*-sulfonation. The mass spectrum showed the molecular ions (M^+, 316, 314) and fragment ions at 279, 215 and 172 corresponding to successive loss of Cl, SO_2Cl and HNCO, respectively.

The IR spectrum indicated the presence of the NH, C=O and SO_2 groups (absorption bands at 3160, 1680 and 1160 cm^{-1}).

Attempts were made to characterize the sulfonyl chloride (29) by reaction with amines to give sulfonamides, which are generally well-defined crystalline solids. The reaction however proved complex; thus reaction with excess dimethylamine appeared to yield not only the expected sulfonamide (30a) but also the product (30b) resulting from a Michael-type addition of the amine across the alkylidene double bond (Chart 3).† The Michael addition product was not observed in the analogous reactions of 5-benzylidenehydantoin *p*-sulfonyl chloride with amines and therefore must arise from the greater polarization of the alkylidene double bond in the arylidene barbituric acids due to the presence of the two adjacent electron-withdrawing carbonyl groups (Chart 3). The aromatic resonances in the ^{1}H NMR spectrum showed two pairs of AA′BB′ doublets suggesting the presence of two different para-disubstituted products, also the singlets at δ 6.0, 10.0 for the protons Hb, Hc and a singlet (δ 8.3) for the alkylidene proton (Ha). The methyl resonances appear as a complex multiplet (δ 2.7–2.4) indicating a mixture of different *N*-dimethyl compounds. The overall ratio of the methyl resonances to the aromatic protons was much too high for (30a). The MS of the products only showed the molecular ion (M^+, 323) corresponding to (30a) due to a retro Michael addition occurring in the mass spectrometer. The elemental analysis data suggested that the major product was (30b).

† As has been suggested by the referee, the Michael addition products (30b, 31–34b, 33, (Chart 3) and 37–39 (Chart 4) may exist as the enol forms  . However, the ^{1}H NMR spectra do not exhibit a low resonance characteristic of the enolic OH group at ca. 17 Hz.

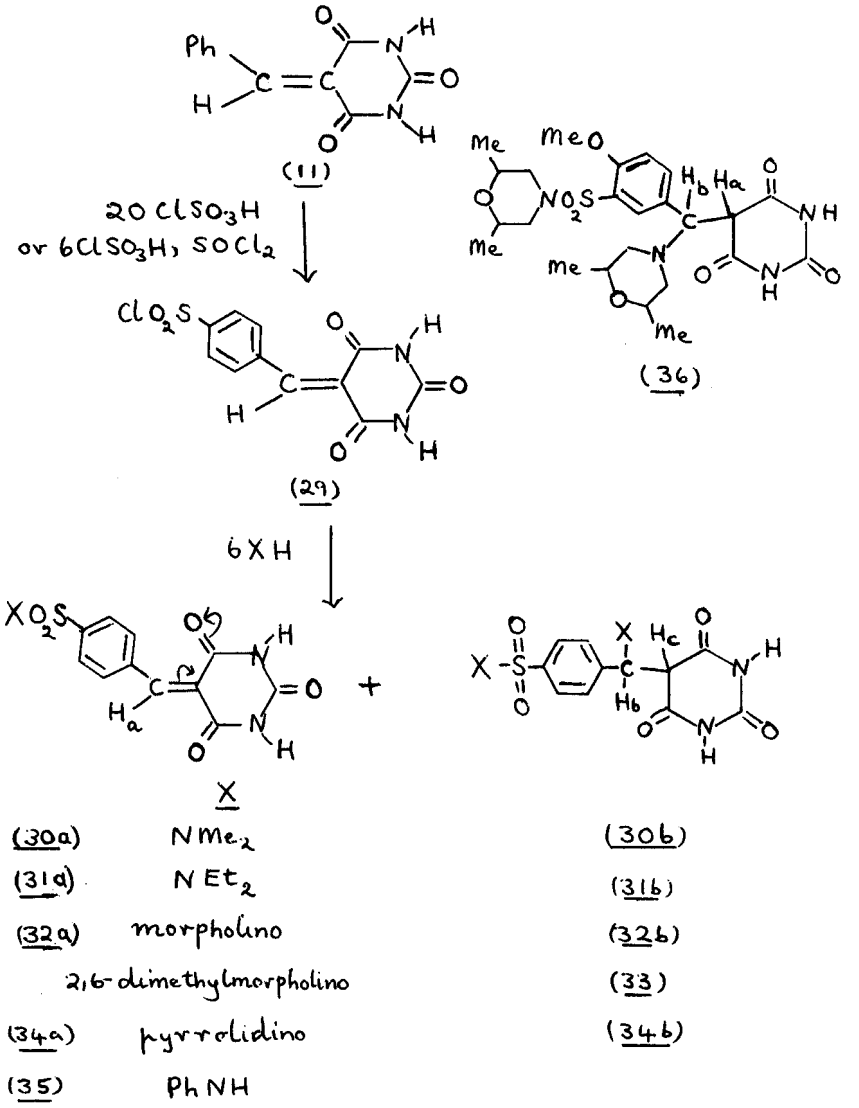
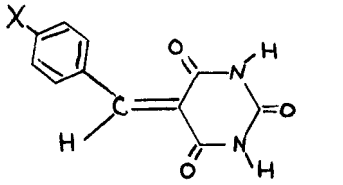


CHART 3 Sulfonyl derivatives of 5-benzylidenebarbituric acid (**11**).

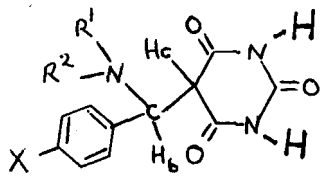
Condensation of (29) with diethylamine again afforded a product which appeared to be a mixture of (31a) and (31b) because the NMR spectrum showed two AA'BB' patterns in the aromatic region (δ 8.10-7.20) with the alkylidene proton (Ha) appearing at δ 8.2 and the proton Hb from the Michael adduct at δ 6.01 and proton Hc at δ 10.0, this is strongly deshielded by the two adjacent carbonyl groups. The mass spectrum only showed the molecular ion (M^+, 351) corresponding to (31a) due to a retro Michael addition reaction occurring in the mass spectrometer.

Spectral and microanalytical data for the product from reactions of (29) with morpholine indicated that it was also a mixture of the benzylidenesulfonamide



(11), X=H ; (14), X=OMe

R' R² NH



	X	R'	R²
(37)	H	Me	Me
(38)	H	Et	Et
(39)	OMe	Et	Et

CHART 4 Michael adducts of 5-arylidenebarbituric acids with amines.

(32a) and the corresponding Michael adduct (32b). The NMR spectrum indicated an aliphatic/aromatic proton ratio of 3:1 in between that for (32a) of 2:1 and for (32b) (4:1). On the other hand, the reaction of (29) with 2,6-dimethylmorpholine appeared to give a low yield of the sulfonamido Michael adduct (33) as the sole product since the NMR spectrum showed the aromatic resonances (δ 7.54–7.25) as a multiplet consisting of only one AA'BB' pattern. The resonance at δ 6.01 (H_b) and the observed ratio of methyl: aromatic protons (3:1) was also in agreement with the structure (33).

Condensation of (29) with pyrrolidine gave a mixture of (34a) and (34b) from examination of the NMR spectrum (two AA'BB' patterns in the aromatic resonances (δ 8.5–7.5).

The reaction of (29) with the more bulky and less reactive aniline afforded the benzylidenesulfonamide (35); here the NMR spectrum showed only one AA'BB' pattern (two doublets at δ 7.25, 7.18). MS showed the molecular in (M^+, 371) and the microanalytical data were in reasonable agreement with the assigned structure.

Attempts were made to chlorosulfonate other 5-arylidenebarbituric acids: treatment of 5-(*p*-methoxybenzylidene) barbituric acid (14), the 5-cinnamylidene (23) and the 2-thienylidene (26) derivatives with chlorosulfonic acid afforded the corresponding sulphonyl chlorides. However, no pure products could be isolated from the reaction of chlorosulfonic acid on *o*- and *m*-methoxybenzylidene-(12, 13), biphenylidene-(22) and α-naphthylidene (28)-barbituric acids. 5-Arylidenebarbituric acids are claimed[15] to undergo a Michael addition reaction with compounds containing a reactive methylene group, e.g., nitromethane and cyclohexanone. However, the addition of amines across the alkylidene double bond has not been previously reported. The reaction of 5-benzylidene (11)- and 5-(*p*-methylbenzylidene) barbituric acid (14) with dimethylamine and diethylamine (3 molar equivalents) was therefore investigated. The Michael adducts (37–39 Chart 4)† were isolated and the structures confirmed by NMR spectroscopy and microanalytical data.

The NMR spectra of the diethylamines (38, 39) showed the protons Hb and Hc as singlets (δ 6.0, 10.0, respectively) and the characteristic splitting pattern for protons of the *N*-ethyl group at δ 2.8, 1.1.

The mass spectra only showed the molecular ions corresponding to the parent arylidene barbituric acids probably due to a retro-addition reaction occurring in the mass spectrometer.

The UV spectra of the 5-arylidene derivatives (11) and (14) showed the long wave length absorption bands at 326 and 366 nm, respectively which are associated with the conjugated Ar—CH=CH—C(=O)-system.[7] These bands were absent in the adducts (37, 39) confirming that addition has occurred across the alkylidene double band.

EXPERIMENTAL

Melting points were determined using a Gallenkamp electric apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded with a Bruker AC 250 spectrometer using tetramethylsilane as internal standard and deutero dimethylsulfoxide as solvent. Resonances indicated by an asterisk were reduced by D_2O treatment. IR spectra were recorded as K Br discs using a Perkin Elmer 237 spectrophotometer. Mass spectra were determined with a VG micromass V15 spectrometer operating at 70 ev. TLC was carried out using Camlab silica gel plates sensitized to UV 256 nm and petroleum ether-ethyl acetate (2:3) as eluant.

Chlorosulfonation of 5,5-diphenylhydantoin (1). The hydantoin (1) (10 g, 0.042 mole) was gradually added to chlorosulfonic acid (31.6 ml, 0.48 mole) and the solution was refluxed for 4 hours. The mixture was allowed to cool to room temperature and thionyl chloride (20 ml) and dimethylformamide (3 drops) added. The solution was left at room temperature for 5 days and added to crushed ice. The precipitate was filtered off, washed with cold water and dried in a vacuum desiccator to give bis-sulfonyl chloride (2), (22.8 g, 88%), m.p. 242–244°C. TLC showed one spot R_F 0.80. IR: υ_{max} 1660 (C=O), 1610 (ArC=C), 1360, 1150 (SO_2) cm^{-1}. MS: 415, 413 (M^+ − Cl), 407, 405 (M^+ − CONH), 372, 370 (M^+ − CONH, −Cl) 344, 342 (M^+ − CONH, Cl, −CO), 179. ^{1}H-NMR: δ 11.2* (*s*, 2H, NH), 7.75–7.20 (*m*, 8H, ArH).

General procedure for the preparation of the 5,5-diphenylhydantoin-bis-sulfonamides (3–10). The bis-sulfonyl chloride (2) (3 g, 0.007 mole) was suspended in methanol (20 ml) and the appropriate amine (approx. 0.042 mole) was gradually added until the mixture was just alkaline. The solution was left overnight at room temperature and poured onto crushed ice-water (200 ml), and the mixture acidified (dilute HCl). The resultant precipitate was filtered off, washed with water and recrystallised from methanol to give the sulfonamide.

Compound (5)
TLC showed one spot, R_F 0.40. IR υ_{max} 1670 (C=O), 1600 (ArC=C), 1350, 1140 (SO_2) cm^{-1}. MS: M^+ (466), 442 ($M^+ - NMe_2$), 359 ($M^+ - SO_2NMe_2$). ^1H NMR: δ 9.3* (*s*, 2H, NH), 7.85–7.50 (*m*, 8H, ArH), 2.60, 252 (2 × *s*, 12H, NMe_2). ^{13}C NMR: δ 186, 156 (CO), 141–125 (10 signals, Ar—C), 40 (CH_3).

Compound (7)
TLC showed one spot, R_F 0.32. IR υ_{max} 1660 (C=O), 1590 (ArC=C), 1340, 1160 (SO_2) cm^{-1}. MS: M^+ (518), 448 (M^+ − pyrrolidine), 384 ($M^+ - SO_2C_4H_8N$).

Compound (9)
TLC showed one spot, R_F 0.25. IR υ_{max} 1665 (C=O), 1600 (ArC=C), 1340, 1160 (SO_2) cm^{-1}. MS: M^+ (550), 507 (M^+ − CONH), 464 ($M^+ - C_4H_8NO$), 400 ($M^+ - SO_2C_4H_8NO$). ^1H NMR δ 9.60* (*s*, 2H, NH), 8.0–7.80 (*m*, 8H, ArH), 3.80–2.80 (*m*, 16H, morpholino H).

General procedure for preparation of 5-arylidenebarbituric acids (11–28). Barbituric acid (6.4 g, 0.05 mole) was dissolved in water (100 ml) on the steam bath. A solution of the aromatic aldehyde (0.06 mole) dissolved in warm ethanol was gradually added with stirring. The product generally rapidly began to precipitate out from the hot solution. When all the aldehyde had been added, the suspension was heated for a further 1 hour and allowed to cool to room temperature. The mixture was diluted with ethanol (25 ml), stirred and cooled (5°C). The precipitate was filtered off, washed with hot water, ethanol and ether and dried under the IR lamp to give the corresponding 5-arylidenebarbituric acid.

Compound (12)
IR υ_{max} 3200 (NH), 1740, 1680 (C=O), 1590 (ArC=C) cm^{-1}. ^1H NMR: δ 11.4*, 11.2* (2 × *s*, 2H, NH), 8.5 (*s* 1H, alkylidene H_a), 8.0–7.0 (*m*, 4H, ArH), 3.8 (*s*, 3H, OMe). MS: 246 (M^+), 215 ($M^+ - OCH_3$), 200 (M^+ − CONH), 172 (M^+ − CONH, −CO).

Compound (19)
^1H NMR δ 11.65*, 11.4* (2 × *s*, 2H, NH), 8.2 (*s*, 1H, Ha), 7.60–7.40 (*m*, 3H, ArH). MS: 251, 249 (M^+ − Cl), 206 (M^+ − Cl, −CONH), 177, 162, 150, 135, 114, 99, 85, 43.

Compound (21)
^1H NMR: δ 11.5*, 11.4* (2 × *s*, 2H, NH), 8.6 (*s*, 1H, Ha), 7.70–7.35 (*m*, 4H, ArH, AA'BB' pattern). MS: 284 (M^+), 265, 240, 215, ($M^+ - CF_3$), 197, 172, 170, 151, 120, 75.

Compound (26)
^1H NMR 11.4*, 11.2* (2 × *s*, 2H, NH), 8.6 (*s*, 1H, Ha), 8.3–7.4 (*m*, 3H, thiophen H).

Chlorosulfonation of 5-benzylidenebarbituric acid (11). Method 1: Ice-cold chlorosulfonic acid (90 ml, 1.4 mole) was gradually added to 5-benzylidenebarbituric acid (11) (15 g, 0.07 mole) with vigorous stirring. After 1 week at room temperature, the solution was poured onto crushed ice (200 g). When the ice had melted, the precipitate was filtered off, washed with cold water (3 × 100 ml), and dried *in vacuo* to yield the sulfonyl chloride (29) (18.6 g, 85%), m.p. 125°C (decomp).

Method 2: Ice-cold chlorosulfonic acid (18 ml, 0.28 mole) was added dropwise to 5-benzylidenebarbituric acid (10 g, 0.046 mole) followed by thionyl chloride (10 ml) with swirling. The mixture was left one week at room temperature to give the sulfonyl chloride (29) (11.6 g, 80%), m.p. 180°C (decomp). (Found: C, 42.3; H, 2.4; N, 8.5; S, 11.6. $C_{11}H_7Cl\,N_2O_5S$ requires C, 42.0; H, 2.2; N, 8.9; S 10.2%). IR: υ_{max} 3160 (NH), 1680 (C=O), 1160 (SO_2) cm^{-1}. MS: 316, 314 (M^+), 279 (M^+ − Cl), 215 ($M^+ - SO_2Cl$), 172 (M^+ − Cl, $-SO_2Cl$ − HNCO), 36 (HCl). ^1H NMR: δ 11.4*, 11.3* (2 × *s*, 2H, NH) 10.0 (*s*, 1H, H_c), 8.3 (*s*, 1H, alkenic Ha), 8.0–7.6 (*m*, 4H, AA'BB' pattern, ArH).

Condensation of (29) *with amines*. a) Reaction with dimethylamine: A solution of dimethylamine (40% aqueous solution, 4.25 ml, 0.037 mole) in methanol (20 ml) was added dropwise to the sulfonyl chloride (29) (2 g, 0.0063 mole) at 0°C with stirring. The solution was left for one week at room temperature, acidified and added to ice-water (100 ml). The precipitate was collected, washed with acetone and ether and dried *in vacuo* to give a white powder (a mixture of 30a and 30b), m.p. 175–180°C (decomp). (Found: C, 46.4; H, 5.7; N, 14.3. 30a, $C_{13}H_{20}N_3O_5S$ requires C 48.3; H, 4.0; N, 13.0. 30b, $C_{15}H_{20}N_4O_5S\,1H_2O$ requires C, 46.6; H, 5.7; N, 14.5%). IR: υ_{max} 3200 (NH), 1700 (C=O), 1600 (ArC=C), 1360, 1160 (SO_2) cm^{-1}. ^1H NMR: δ 11.4*, 11.2* (2 × *s*, 2H, HN), 8.5 (*s*, Ha), 8.0–7.7 (*m*, 4H, ArH), 6.0 (*s*, Hb), 2.7–2.4 (*m*, NMe_2). MS: 323 (M^+ for 30a), 279 ($M^+ - NMe_2$), 215 ($M^+ - SO_2NMe_2$), 172, 44.

b) Reaction with diethylamine: 5-Benzylidenebarbituric acid *p*-sulfonyl chloride (29) (3.9 g, 0.0125 mole) was gradually added to a solution of diethylamine (3.86 g, 0.05 mole) in acetonitrile (20 ml). The mixture was stirred for 2 hours and then left at room temperature for 2 days. The solution was added to ice (100 g); the precipitate was collected, acidified with 1 M-hydrochloric acid, washed with acetone and ether, and dried *in vacuo* to give white crystals (31a, 31b) (0.3 g), m.p. 220°C (decomp).

(Found: C, 51.2; H, 6.8; N, 12.4. (31a), $C_{15}H_{17}N_3O_5S$ requires C, 51.3; H, 4.9; N, 12.0 (31b), $C_{19}H_{28}N_4O_5S$ $1H_2O$ requires C, 51.6; H, 6.8; N, 12.7%. ^1H NMR: δ 10.2* (*s*, 2H, NH), 10.0 (*s*, 1H, H_c), 8.2 (*s*, Ha), 8.10–7.2 (*m*, ArH, 2 AA'BB' patterns), 6.01 (*s*, H_b), 3.21–3.13 (*m*, $\underline{CH_2}$ CH_3), 1.08 (*m*, CH_2 $\underline{CH_3}$). MS: 351 (M^+ for 31a), 336 (M^+ – Me), 279 (M^+ – NEt_2), 253, 215 (M^+ – SO_2NEt_2), 196, 172, 128, 58, 42.

c) Reaction with morpholine: A similar procedure afforded a product (32a, 32b), (54%), m.p. 220–225°C (decomp). (Found: C, 47.1; H, 5.4; N, 11.6. (32a), $C_{15}H_{15}N_3O_6S$ requires C, 49.3; H, 4.1; N, 11.5. (32b), $C_{19}H_{24}N_4O_7S$ $1H_2O$ requires C, 48.5; H, 5.5; N, 11.9%. ^1H NMR δ 9.25* (br *s*, 2H, NH), 8.4 (*s*, Ha), 8.20–7.20 (*m*, ArH), 6.0 (*s*, Hb), 3.7–2.4 (*m*, morpholino H).

d) Reaction with 2,6-dimethylmorpholine: The product (33) was a white crystalline solid (26%), m.p. 214–217°C. (Found: C, 52.0; H, 6.6; N, 10.4. (33), $C_{23}H_{32}N_4O_7S$ $1H_2O$ requires C, 52.6; H, 6.3; N, 10.7%). ^1H NMR: δ 10.05* (*s*, 1H, NH), 9.79* (*s*, 1H, NH), 7.54–7.25 (*m*, 4H, ArH, AA'BB' pattern), 6.04 (*s*, 1H, H_b), 3.74–1.80 (*m*, 24H, morpholino H), 1.11, 1.03 (2 × *d*, 12H, CH_3). MS: 393 (M^+ – $C_6H_{13}NO$), 279 (M^+ – Me), 215 (M^+ – $C_6H_{13}NO$, $-SO_2$), 114, 42.

e) Reaction with pyrrolidine: The product (34a, 34b) was an off-white solid (25%), m.p. 180–185°C (decomp). ^1H NMR: δ 11.5*, 11.30* (2 × *s*, 2H, NH), 8.5–7.5 (*m*, ArH, Ha), 3.6–2.4 (pyrrolidino H). MS: 349 (M^+ of 34a), 215 (M^+ – $SO_2NC_4H_9$), 70 (pyrrolidine).

f) Reaction with aniline: The sulfonyl chloride (29) (6.29 g, 0.02 mole) was stirred with triethylamine (2.02 g, 0.02 mole) and redistilled aniline (1.86 g, 0.02 mole) at room temperature (2 hours). The mixture was neutralized with dilute hydrochloric acid and poured onto ice-water with stirring. The precipitate was filtered off, washed with water, acetone and ether to give a fawn powder (35) (3.84 g, 52%), m.p. 221–223°C. (Found: C 54.7; H, 3.8, N, 11.0. $C_{17}H_{13}N_3O_5S$ requires C, 55.0; H, 3.5; N, 11.3%). IR: υ_{max} 3250, 3180 (NH), 1700 (C=O), 1595 (ArC=C), 1360, 1160 (SO_2) cm^{-1}. ^1H NMR: δ:11.3*, 11.1* (2 × *s*, 2H, NH), 9.9* (*s*, 1H, PhNH), 7.82–7.20 (*m*, 9H, ArH). MS: 371 (M^+), 215 (M^+ – $C_6H_5NHSO_2$), 93 ($PhNH_2$).

Chlorosulfonation of 5-(4'-methoxybenzylidene) barbituric acid (14). The barbituric acid (5 g, 0.02 mole) was added to chlorosulfonic acid (15 ml, 0.23 mole) at 0°C and the solution left at room temperature for 2 days, then thionyl chloride (5 ml) and dimethylformamide (2 drops) was added. After 3 hours, the mixture was added to ice-water to give the 3'-sulfonyl chloride as a yellow solid (7g, 80%), m.p. 205°C (decomp). (Found: C, 39.4; H, 2.9; N, 7.3. $C_{12}H_9ClN_2O_6S$. 1 H_2O requires: C, 39.7; H, 3.0; N, 7.7%). MS showed the molecular ions (M^+, 346, 344).

The product (1 g) was characterized by reaction with 2,6-dimethylmorpholine (1.5 ml, 5 molar equivalents) in ethanol (10 ml) for 12 hours to give the sulfonylmorpholidate (36) as an orange powder (0.5 g), m.p. 175° (decomp). (Found: C, 51.1; H, 6.6; N, 10.4. $C_{22}H_{33}N_4O_8S$ requires C, 51.5; H, 6.4; N, 10.9%).

Chlorosulfonation of 5-cinnamylidenebarbituric acid (23). 5-Cinnamylidenebarbituric acid (5 g, 0.02 mole) was reacted with chlorosulfonic acid (24 g, 0.21 mole) for 5 days, then thionyl chloride (20 ml) and dimethyl formamide (2 drops) was added. The mixture was left for 12 hours and poured onto ice to give the *para*-sulfonyl chloride (3.5 g), m.p. 298–300°C (decomp). (Found: C, 45.4; H, 2.7; N, 7.9. $C_{13}H_9ClN_2O_5S$ requires C, 45.8; H, 2.6; N, 8.2%). IR: υ_{max} 3200 (NH), 1685 (CO), 1595 (ArC=C), 1370, 1160 (SO_2) cm^{-1}. MS showed the molecular ions (M^+ 342, 340).

Chlorosulfonation of 2-thienylidenebarbituric acid (26). The barbituric acid (5.5 g, 0.025 mole) was reacted with chlorosulfonic acid (23.3 g, 0.20 mole) for 2 hours at room temperature. The solution was added to ice (100 g), the precipitate was filtered off and washed with cold water.

The crude sulfonyl chloride (4 g, 0.0125 mole) was dissolved in acetonitrile (30 ml) and diethylamine (1.83 g, 0.250 mole) added dropwise. The mixture was left at room temperature (2 hours) to give the 6'-diethylsulfonamide as a yellow powder (0.7 g, 15%), m.p. 320°C (decomp). (Found: C, 44.2; H, 3.2; N, 11.5. $C_{13}H_{15}N_3O_5S_2$ requires C, 43.7; H, 4.2; N, 11.8%). ^1H NMR: δ 11.8*, 11.3* (2 × *s*, 2H, NH), 8.7 (*s*, 1H, alkylidene H_a), 8.4–7.3 (*m*, 3H, thiophen H), 2.9 (*q*, 4H, $N\underline{CH_2}CH_3$), 1.1 (*t*, 6H, N $CH_2\underline{CH_3}$).

Michael addition of amines to 5-arylidenebarbituric acids. The 5-arylidenebarbituric acid (5.4 g, 0.025 mole) was suspended in acetonitrile (30 ml) and a solution of the amine (0.075 mole) dissolved in acetonitrile (20 ml) was gradually added with stirring. The suspension was stirred for 3 hours and left overnight at room temperature. The mixture was added to cold water and acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water (3 × 15 ml) and dried in a vacuum desiccator and finally under the IR lamp to give the product. By this general procedure, 5-benzylidenebarbituric acid (11) was treated with dimethylamine to give the adduct (37) as a cream powder (80% yield), m.p. 230°C. (Found: C, 56.0; H, 6.2; N, 15.2. $C_{13}H_{15}N_3O_3$ requires C, 55.9; H, 6.2; N, 15.2%).

IR: υ_{max} 3500 (OH), 3200 (NH), 1670 (C=O), 1600 (ArC=C), cm^{-1}. MS: 216 ($M^+ - NMe_2$), 172 ($M^+ - NMe_2$, $-HNCO$).

Compound (11) was also reacted with diethylamine to give the corresponding adduct (38) as a pale yellow powder (84%), m.p. 211°C (Found: C, 58.2; H, 6.4; N, 14.2. $C_{15}H_{19}N_3O_3$. $1H_2O$ requires C, 58.6; H, 6.8; N, 13.7). IR: υ_{max} 3230, 3140 (NH), 1700 (C=O), 1595 (ArC=C) cm^{-1}. ^1H NMR: δ 11.2* (2 × *s*, 2H, NH), 10.0 (*s*, 1H, Hc) 7.95–7.1 (*m*, 5H, ArH), 6.0 (*s*, 1H, Hb), 2.8 (*q*, 4H, $\underline{CH_2}CH_3$), 1.15 (*t*, 6H, $CH_2\underline{CH_3}$). MS: no molecular ion at 289, only $M^+ - NEt_2$ at 216.

5-(*p*-Methoxybenzylidene) barbituric acid (14) was reacted with diethylamine to give the adduct (39) as a yellow powder (72%), m.p. 220–223°C. (Found: C, 56.5; H, 6.4; N, 12.1. $C_{16}H_{21}N_3O_4$. $1H_2O$ requires C, 56.9; H, 6.8; N, 12.4%). ^1H NMR: δ 11.2* (*s*, 2H, NH), 10.0 (*s*, 1H, H_c), 7.90–6.75 (*m*, 4H, ArH), 6.0 (*s*, 1H, H_b), 3.8 (*q*, 4H, $\underline{CH_2}CH_3$), 1.10 (*t*, 6H, $CH_2\underline{CH_3}$).

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