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SYNTHESIS OF SOME NOVEL BENZYLIDENEHYDANTOINS: AMINO ACIDS DERIVATIVES

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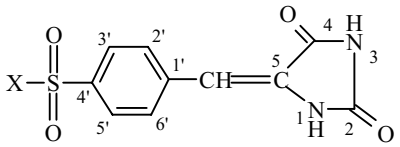
5-Benzylidenehydantoin reacts with chlorosulfonic acid to give the corresponding p-sulfonyl chloride. Condensation of the latter with amino acids leads to sulfonylamino acid derivatives, which on coupling with glycine methyl ester hydrochloride in THF–Et_3N using the dicyclohexylcarbodiimide method furnish the desired dipeptide methyl esters. The spectral data of the compounds are briefly discussed.

Keywords: 5-(*p*-chlorosulfonylbenzylidene)hydantoin, N-[(*p*-hydantoinylidenemethyl)benzenesulfonyl] derivatives of amino acids, and dipeptides.

This work is a part of our general program on the chemistry and biological activity of aryl sulfonyl derivatives [1-6]. We have demonstrated that compounds like cinnamic acid [7-8] are readily chlorosulfonated. 5-Benzylidenehydantoin should therefore be a suitable substrate for chlorosulfonation. The sulfonylamino acid derivatives possess potential biological activity since several 5-substituted hydantoins are valuable anticonvulsant drugs [9], and hydantoins also show fungicidal and herbicidal activity [10-11].

Hydantoins are known [10] to react with aromatic aldehydes to give the corresponding 5-benzylidene derivatives. Boyd and Robson [12] observed that the condensation occurs in pyridine in the presence of diethylamine or piperidine, the former being a more effective condensing agent. The reaction was also carried out in pyridine alone [13, 14], glacial acetic acid–sodium acetate [15, 16], or ethanolamine–sodium hydroxide [17].

5-Benzylidenehydantoin was obtained in 55% yield following the procedure of Boyd and Robson [12]; the use of either piperidine or ethanolamine gave a much lower yield (25%). The chlorosulfonation of 5-benzylidenehydantoin has not been reported previously. The optimum conditions involved treatment of the substrate with a large excess of chlorosulfonic acid (16 equivalents) at room temperature for 6 hours to give an excellent yield (87%) of sulfonyl chloride **1**. Reaction with less reagent (3 equivalents) in excess thionyl chloride afforded a mixture which may arise from the initial chlorination of CONH groups.



1 X = Cl, **2**–**12** X = R (cf. Table)

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TABLE 1. Physical Data for the Sulfonylbenzylidenehydantoin Amino Acid and Dipeptide Derivatives (**2-12**)

Compound	Empirical formula	Calculated, % / Found, %				R	R_f	mp, °C*	Yield, %
		C	H	N	S				
2	$C_{12}H_{11}N_3O_6S$	44.31 44.30	3.38 3.35	12.92 12.90	9.85 9.80	Gly	0.80	274-276	70
3	$C_{13}H_{13}N_3O_6S$	46.02 46.00	3.83 3.81	12.39 12.31	9.44 9.41	DL-Ala	0.83	270-272	68
4	$C_{13}H_{13}N_3O_6S$	46.02 46.00	3.83 3.81	12.39 12.36	9.44 9.40	β-Ala	0.82	280-282	75
5	$C_{15}H_{17}N_3O_6S$	49.05 49.00	4.63 4.61	11.44 11.40	8.72 8.70	DL-Val	0.78	290-292	65
6	$C_{16}H_{17}N_3O_7S$	50.39 50.33	4.99 4.96	11.02 11.00	8.40 8.40	DL-Leu	0.77	275-277	72
7	$C_{19}H_{17}N_3O_7S$	52.90 52.90	3.94 3.90	9.74 9.71	7.42 7.41	L-Tyr	0.81	248-250	88
8	$C_{15}H_{16}N_4O_7S$	44.55 44.50	3.96 3.93	15.84 15.81	7.92 7.91	Gly-GlyOMe	0.76	208-210	53
9	$C_{16}H_{18}N_4O_7S$	45.93 45.90	4.31 4.31	15.31 15.30	7.65 7.63	DL-Ala-GlyOMe	0.83	220-222	45
10	$C_{16}H_{18}N_4O_7S$	45.93 45.93	4.31 4.31	15.31 15.30	7.65 7.63	β-Ala-GlyOMe	0.85	216-218	77
11	$C_{18}H_{22}N_4O_7S$	48.43 48.40	4.93 4.90	14.35 14.31	7.17 7.13	DL-Val-GlyOMe	0.86	200-202	55
12	$C_{19}H_{24}N_4O_7S$	49.56 49.50	5.22 5.20	13.91 13.90	6.96 6.95	DL-Leu-GlyOMe	0.87	196-198	60

* Cryst. solvent: methanol–water.

Compound **1** was condensed with a number of amino acids under standard conditions to give amino acid derivatives **2-7**. Some of the coupling products **2-6** were converted into dipeptide methyl esters **8-12** by reaction with glycine methyl ester hydrochloride using the dicyclohexyl carbodiimide (DCC) method. The physico-chemical characteristics of compounds **8-12** are presented in Table 1.

All the compounds synthesized had IR, NMR, and mass spectra consistent with the assigned structures.

The IR spectra of the hydantoins exhibited two absorption bands at approximately 1780 and 1720 cm^{-1} in agreement with the literature [10], and the sulfonyl derivatives showed two additional bands at 1370 and 1160 cm^{-1} associated with the SO_2 group.

In the mass spectra, the majority of the compounds showed the molecular ions (M^+), most of the amino acid derivatives suffered extensive fragmentation, and the molecular ions were generally observed with these derivatives [18].

The NMR spectra of the 5-benzylidenehydantoins showed that the N-3 and N-1 protons appeared at approximately δ 11.3 and 10.5, so that the former was the more deshielded, although the difference is less than generally observed [19] for hydantoins without the 5-benzylidene group [10, 19].

EXPERIMENTAL

Melting points were taken on a Griffin melting point apparatus and are uncorrected. Infrared spectra of solid samples (KBr discs) were run on a Schimadzu model 440 spectrophotometer. ^1H NMR spectra were measured in DMSO-d_6 as solvent using an FX 90 Q Fourier Transform ^1H NMR spectrometer. Mass spectra were obtained using a Schimadzu GC-MS QP 1000 Ex spectrometer with the direct inlet system. TLC analyses were carried out on Merck silica gel plates and developed with *n*-butanol–acetic acid–water (4:1:1) using iodine, ninhydrin, and benzidine as spraying agents.

5-(*p*-Chlorosulfonylbenzylidene)hydantoin (1) was prepared according to the procedure described earlier [20].

Preparation of N-[(*p*-Hydantoinylidenemethyl)benzenesulfonyl]amino Acids (2–7) (General Procedure). To amino acid (0.1 mol) in a mixture of water (25 ml) and THF (15 ml) triethylamine (5 ml) was added followed by portionwise addition of sulfonyl chloride **1** (0.11 mol) during 30 min. The temperature of the reaction mixture during the process of addition was kept at 10°C. Stirring continued for 2 h at 20°C. Tetrahydrofuran was removed by concentration of the reaction mixture under reduced pressure, water (30 ml) was added, the mixture was acidified with 2M HCl to pH 5, and the crude products were filtered off and recrystallized. All the products **2–7** (see Table) were chromatographically homogeneous (iodine and benzidine development).

IR of compound **2**, ν, cm^{-1}: 3280, 3175 (NH), 1985, 1720 (C=O), 1660 (aliph. C=C), 1595 (aryl C=C), 3260, 1370, 1170 (SO_2NH), 2850 (COOH), 1350, 1150 (SO_2).

MS of compound **2** *m/z* 325 (M^+).

^{1}H NMR of compound **5** (DMSO-d_6), δ: 11.15 (1H, 3-H); 9.75 (1H, 1-H); 7.65 (4H, Ar-H); 6.35 (1H, CH=); 4.26 (1H, α-CH–Val); 1.97 (1H, β-CH–Val); 0.98 (6H, $(CH_3)_2$), 11.3, (1H, COOH).

Synthesis of Sulfonyl Dipeptide Methyl Esters 8-12 (General Procedure). To a stirred solution of glycine methyl ester hydrochloride (0.016 mol) in THF (100 ml) triethylamine (5 ml) was added and then, at 0°C, sulfonylamino acid **2-6** (0.008 mol) in THF (50 ml) and dicyclohexylcarbodiimide DCC (1.62 g) were added to the above mixture. The reaction mixture was stirred for 2 h at 0°C and for another 2 h at room temperature. The precipitated dicyclohexylurea was filtered off, acetic acid (1 ml) was added to the solution, and the mixture was left standing overnight. The precipitate was filtered off and the remaining solution was distilled off under vacuum. The remaining solid was recrystallized from aqueous ethanol or methanol. The products **8-12** were chromatographically homogeneous.

IR of compound **9**, ν, cm^{-1}: 3390 (NH), 3280, 1370, 1170 (SO_2NH), 1665, 1530, 1280 (amide I, II, III), 1445, 1360 ($COOCH_3$), 1760 (C=O), 1310, 1160 (SO_2).

^{1}H NMR of compound **9** (DMSO-d_6), δ: 7.86 (1H, SO_2NH); 8.04 (1H, CONH); 3.87 (3H, $COOCH_3$); 4.34 (1H, α-CH Ala); 1.22 (3H, CH_3 Ala), and other bands supporting the structure of a dipeptide.

MS of compound **9** *m/z* 418 (M^+).

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