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Sulfur containing activated hydantions. Synthesis and screening some novel benzylidenehydantoins amino acids derivatives

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5-Benzylidenehydantoin reacts with chlorosulfonic acid to give the corresponding *p*-sulfonyl chloride **1**. Condensation with nucleophiles gives amino acid derivatives **2–7**. Coupling reactions of some amino acid derivatives (**2–6**) with amino acid methyl ester hydrochloride in THF-Et_3N medium using the dicyclohexylcarbodiimide method (DCC) furnish the desired dipeptide methyl esters **8–12**. The spectral data of the synthesized compounds are briefly discussed.

Keywords: benzylidenehydantoins amino acids, dipeptide derivatives.

INTRODUCTION

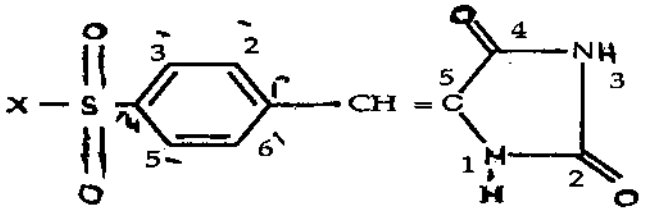
This work forms part of our general programme on the chemistry and biological activity of aryl sulfonyl derivatives.[1–6] It has been demonstrated that compounds like cinnamic acid[7,8] are readily chlorosulfonated due to the activating influence of the olefinic double bond. 5-Benzylidenehydantoin should therefore provide suitable substrates for chlorosulfonation. The sulfonylamino acid derivatives possess potential biological activity since several 5-substituted hydantoins are valuable anti-convulsant drugs,[9] and hydantoins also show fungicidal and herbicidal activity.[10,11]

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

RESULTS AND DISCUSSION

5-Benzylidenehydantoin was obtained in 55 % yield following the procedure of Boyd and Robson.[12] The use of either piperidine or ethanolamine gave much lower yields (25 %). The chlorosulfonation of 5-benzylidenehydantoin has not been previ-

ously reported. The optimum conditions involved treatment of the substrate with a large excess of chlorosulfonic acid (16 equivalents) at room temperature for 6 h to give an excellent yield (87 %) of the corresponding sulfonyl chloride **1**.



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

Reaction with less reagent (3 equivalents) in excess thionyl chloride afforded a mixture which may arise from initial chlorination of the CO.NH group.

Compound **1** was condensed with a range of nucleophilic reagents, such as amino acids, under standard conditions to give amino acid derivatives **2**–**7**. Some coupling products **2**–**6** were converted into dipeptide methyl esters **8**–**12** by reaction with an amino acid methyl ester hydrochloride using the dicyclohexylcarbodiimide method (DCC).

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

The mass spectra of the majority of the compounds showed the molecular (M^+), since 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 11.3 and 10.5 indicating 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 were run as KBr disks on a Schimadzu model 440 spectrophotometer. ^{1}H-NMR spectra were measured in DMSO-d_6 as solvent unless otherwise stated using Fx 90 Q Fourier Transform ^{1}H-NMR spectrometer. Mass spectra were obtained using a Schimadzu. GC. M. S. QP 1000 Ex spectrometer using 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-*chlorosulfonyl benzylidenehydantoin (1)*

The title compound was prepared according to the procedure described earlier.[20]

Coupling reactions (2–7)

General procedure. To an amino acid (0.1 mol) in a water (25 ml) THF (15 ml) mixture was added triethylamine (5 ml). Sulfonylchloride (0.11 mol) was then added portionwise during 30 min, whereby the temperature of the reaction mixture was kept at 10 ºC. Stirring was continued for 2 h at 20 ºC. The

tetrahydrofuran was removed from the reaction mixture under reduced pressure, water (30 ml) was added and acidified with 2 M HCl to pH 5. The crude products were filtered off and recrystallized. All the products (**2–7**) were found to be chromatographically homogeneous on iodine and benzidine development.

cf. Table I. Compds. **2–7**.

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

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

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

*Synthesis of sulfonyl dipeptide methyl esters **8–12***

General procedure. To a solution of amino acid methyl ester hydrochloride (0.016 mol) in THF (100 ml) was added triethylamine (5 ml). This mixture was cooled to 0 ºC, and the sulfonylamino acid (**2–6**) (0.008 mol) in THF (50 ml), and dicyclohexylcarbodiimide, DCC (1.62 g) added under stirring. The reaction mixture was stirred for 2 h at 0 ºC and for another 2 h at room temperature. The precipitated dicyclohexylurea was filtered off, acetic acid (1 mol) added and the solution left standing overnight. The precipitate was filtered off and the solution distilled under vacuum. The remainig solid was recrystallized from (ethanol–water). The products **8–12** were found to be chromatographically homogeneous.

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

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

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

TABLE I. Physical data for the sulfonylbenzylidenehydantoins amino acid and dipeptide derivatives **2–12**

Group No.	R	M.p. ºC	Yield %	R_f	Molecular formula	Elemental analysis calculated/found			
						%C	%H	%N	%S
2	Gly	274–276	70	0.80	$C_{12}H_{11}N_3O_6S$	44.31	3.38	12.92	9.85
						44.30	3.35	12.90	9.80
3	DL-ala	270–272	68	0.83	$C_{13}H_{13}N_3O_6S$	46.02	3.83	12.39	9.44
						46.00	3.81	12.31	9.41
4	-Ala	280–282	75	0.82	$C_{13}H_{13}N_3O_6S$	46.02	3.83	12.39	9.44
						46.00	3.81	12.36	9.40
5	DL-Val	290–292	65	0.78	$C_{15}H_{17}N_3O_6S$	49.05	4.63	11.44	8.72
						49.00	4.61	11.40	8.70
6	DL-Leu	275–277	72	0.77	$C_{16}H_{19}N_3O_6S$	50.39	4.99	11.02	8.40
						50.33	4.96	11.00	8.40

TABLE I. Contd.

Group No.	R	M.p. °C	Yield %	R_f	Molecular formula	Elemental analysis calculated/found			
7	L-Tyr	248–250	88	0.81	$C_{19}H_{17}N_3O_7S$	52.90	3.94	9.74	7.42
						52.90	3.90	9.71	7.41
8	Gly-GlyOMe	208–210	53	0.76	$C_{15}H_{16}N_4O_7S$	44.55	3.96	15.84	7.92
						44.50	3.93	15.81	7.91
9	DL-Ala-GlyOMe	220–222	45	0.83	$C_{16}H_{18}N_4O_7S$	45.93	4.31	15.31	7.65
						45.90	4.30	15.30	7.63
10	-Ala-GlyOMe	216–218	77	0.85	$C_{16}H_{18}N_4O_7S$	45.93	4.31	15.31	7.65
						45.93	4.31	15.30	7.63
11	DL-Val-GlyOMe	200–202	55	0.86	$C_{18}H_{22}N_4O_7S$	48.43	4.93	14.35	7.17
						48.40	4.90	14.31	7.13
12	DL-Leu-GlyOMe	196–198	60	0.87	$C_{19}H_{24}N_4O_7S$	49.56	5.22	13.91	6.96
						49.50	5.20	13.90	6.95

*Cryst. solvent: (**2–12**) methanol–water

И З В О Д

АКТИВИРАНИ ХИДАНТОНИ КОЈИ САДРЖЕ СУМПОР. СИНТЕЗА И ПОТЕНЦИЈАЛНА БИОЛОШКА АКТИВНОСТ НЕКИХ НОВИХ АМИНОКИСЕЛИНСКИХ ДЕРИВАТА БЕНЗИЛИДЕНХИДАНТОИНА

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5-Бензилиденхидантоин реагује са хлоросулфонском киселином и даје одговарајући *p*-сулфонилхлорид **1**. Његовом кондензацијом са нуклеофилима добивају се деривати аминокиселина **2–7**. Реакцијом купловања неких аминокиселинских деривата (**2–6**) са хидрохлоридом метилестра аминокиселине у THF–Et_3N, применом дициклохексилкарбодиимидне методе (DCC) награђени су жељени метилестри дипептида **8–12**. Укратко су дискутовани спектрални подаци синтетизованих једињења.

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