Synthesis and Anticonvulsant Properties of a Novel Series of 2-Substituted Amino-5-aryl-1,3,4-oxadiazole Derivatives

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A novel series of 2-substituted amino-5-aryl-1,3,4-oxadiazole derivatives were synthesized for their potential anticonvulsant activity. The synthesis involved the cyclodesulfurization of variously substituted salicylthiosemicarbazides with DCCD and mercuric oxide. Representative examples of the title compounds were also prepared by a one-pot cyclodesulfurization of mixtures of salicylhydrazides and phenylisothiocyanate with DCCD.

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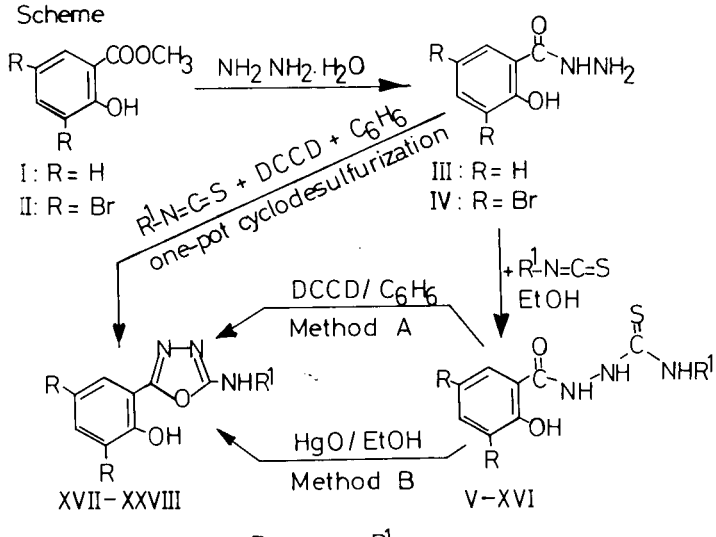
In connection with an extensive program directed towards the synthesis of novel heterocycles of potential biological applications, a variety of substituted benzimidazole [1,2], benzoxazole [3], benzothiazole [1], quinazolone [4] and steroidal-oxazole [5], oxazoline [6] and thiazolidinone [7] derivatives were prepared and the products screened for anticancer [1,2], antimicrobial [4] and endocrinological [5-7] properties. In addition, several fused heterocyclic systems including imidazo[1,5-*a*]benzimidazoles [8], imidazo[1,5-*a*]pyridines [9], triazo[3,4-*a*]phthalazines [10] and triazolo[1,5-*a*][1,3,4]thiadiazines [11] were synthesized and their antihypertensive [10] and anthelmintic [11] activity was evaluated.

Observations that several 1,3,4-oxadiazole derivatives exhibit analgesic [12,13], antiproteolytic [14], antiinflammatory [15], tranquilizing [16], muscle relaxant [17] and CNS depressant [18] properties created an interest in the preparation of the novel series of 2-substituted amino-5-(2'-hydroxy and 2'-hydroxy-3',5'-dibromo)phenyl-1,3,4-oxadiazoles XVII-XXVIII as potential anticonvulsant agents. The synthesis of the title 1,3,4-oxadiazole derivatives XVII-XXVIII was accomplished in accordance with the sequence of reactions depicted in Scheme I. Methyl salicylate (I) and methyl 3,5-dibromosalicylate (II) were fused with excess hydrazine hydrate to produce salicylhydrazide (III) and 3,5-dibromosalicylhydrazide (IV) [19] in high yields. The products were then treated with the appropriate alkyl, aryl and aralkyl isothiocyanates to yield the corresponding 1-salicyl-4-substituted-3-thiosemicarbazides V-XI, as reported [20-23], and 1-(3',5'-dibromo)salicyl-4-aryl-3-thiosemicarbazides XII-XVI, Table I. The reaction of these thiosemicarbazides with 1.5 molar equivalent of dicyclohexylcarbodiimide (DCCD) in boiling benzene or a mixture of benzene and acetone caused their cyclodesulfurization [24] into the corresponding 2-substituted amino-5-aryl-1,3,4-oxadiazoles XVII-XXVIII. When the Nα-substituents were aromatic groups, the products were solid and could be separated as free bases. When they were of aliphatic, alicyclic or aralkyl nature, the oily consistency of the products XXI-XXIII necessitated their identification as picrate salts, Table II.

The 1,3,4-oxadiazoles XVII and XXIV were also synthesized by application of the one-pot cyclodesulfurization reaction [3] of mixtures of the salicylhydrazides III and IV, phenylisothiocyanate and DCCD in boiling benzene. The yield of cyclized products was almost the same in the case of compound XVII, but was much lower in compound XXIV than with the cyclodesulfurization of the thiosemicarbazide XII with DCCD.

Scheme



	R	R^1
V , XVII :	H	C_6H_5
VI , XVIII :	H	$C_6H_4CH_3$(m)
VII , XIX :	H	C_6H_4Cl (p)
VIII , XX :	H	C_6H_4Br (p)
IX , XXI :	H	$C_6H_5CH_2$
X , XXII :	H	$CH_3CH_2CH_2CH_2$
XI , XXIII :	H	C_6H_{11} (cyclo)
XII , XXIV :	Br	C_6H_5
XIII , XXV :	Br	$C_6H_4CH_3$(p)
XIV , XXVI :	Br	$C_6H_4OCH_3$(p)
XV , XXVII :	Br	C_6H_4Cl(p)
XVI , XXVIII :	Br	C_6H_4Br(p)

Table I

Synthesized 1-(3',5'-Dibromo)salicyl-4-aryl-3-thiosemicarbazides (XII-XVI)

Compound	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XII	87	176-177	$C_{14}H_{11}Br_2N_3O_2S$ (445)	37.75	2.47	9.43	38.10	2.70	9.10
XIII	96	179-180	$C_{15}H_{13}Br_2N_3O_2S$ (459)	39.21	2.83	9.15	39.40	2.60	8.80
XIV	92	187-188	$C_{15}H_{13}Br_2N_3O_3S$ (475)	37.89	2.73	8.84	37.60	2.70	8.90
XV	97	171-172	$C_{14}H_{10}Br_2ClN_3O_2S$ (479.5)	35.03	2.08	8.75	34.80	2.30	8.50
XVI	88	178-179	$C_{14}H_{10}Br_3N_3O_2S$	32.06	1.90	8.01	32.00	2.20	7.80

Table II

Synthesized 2-Substituted Amino-5-aryl-1,3,4-oxadiazole Derivatives (XVII-XXVIII)

Compound	Method	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XVII	A	65	223-224	$C_{14}H_{11}N_3O_2$	66.39	4.38	16.59	66.1	4.1	16.4
	B	76		(253)						
XVIII	A	97	183-185	$C_{15}H_{13}N_3O_2$	67.40	4.90	15.72	67.2	5.1	15.6
	B	90		(267)						
XIX	A	91	248-249	$C_{14}H_{10}ClN_3O_2$			14.60			14.5
	B	98		(287.5)						
XX	A	93	258-259	$C_{14}H_{10}BrN_3O_2$	50.60	3.01	12.65	50.9	3.0	12.5
	B	93		(332)						
XXI	A [a]	61	152-153	$C_{21}H_{16}N_6O_9$	50.81	3.25	16.93	50.5	3.1	16.8
				(496)						
	B	85	128-130	$C_{15}H_{13}N_3O_2$	67.40	4.90	15.72	67.3	4.8	15.5
				(267)						
XXII	A [a]	64	137-139	$C_{18}H_{18}N_6O_9$			18.18			18.3
				(462)						
	B	72	103-104	$C_{12}H_{15}N_3O_2$	61.78	6.48	18.02	61.8	6.7	17.9
				(233)						
XXIII	A [a]	60	168-170	$C_{20}H_{20}N_6O_9$			17.21			17.2
				(488)						
	B	85	123-124	$C_{14}H_{17}N_3O_2$	64.84	6.61	16.21	64.9	6.6	16.5
				(259)						
XXIV	A	93	273-274	$C_{14}H_9Br_2N_3O_2$			10.21			10.3
	B	60		(411)						
XXV	A	99	272-273	$C_{15}H_{11}BrN_3O_2$	42.35	2.58	9.88	42.3	2.6	10.0
	B	65		(425)						
XXVI	A	62	223-224	$C_{15}H_{11}Br_2N_3O_3$	40.81	2.49	9.52	40.9	2.4	9.5
	B	60		(441)						
XXVII	A	75	275-276	$C_{14}H_8Br_2ClN_3O_2$	37.71	1.79	9.42	37.8	1.7	9.5
	B	70		(445.5)						
XXVIII	A	75	276-277	$C_{14}H_8Br_3N_3O_2$	34.28	1.63	8.57	34.3	1.6	8.6
	B	72		(490)						

[a] The products were identified as picrate salts.

Moreover, for comparative purposes, the cyclodesulfurization of the thiosemicarbazides V-XVI was carried out by mercuric oxide in boiling ethanol [20,25,26]. The yield of the 1,3,4-oxadiazoles XVII-XXVIII was relatively higher than that obtained by cyclodesulfurization with DCCD especially for compounds XXI-XXIII. In contrast, the yield of compounds XXIV and XXV was much lower in the mercuric oxide cyclodesulfurization processes.

The products were identified by elemental analysis (Tables I and II), ir, ^{1}H nmr and mass spectra. In the ir, the thiosemicarbazides V-XVI showed the bands due to OH, NH, C=O and the mixed vibrational coupling due to

the NCS functions. The spectra of 1,3,4-oxadiazoles XVII-XXVIII on the other hand, lacked the C=O absorption and showed the OH, NH and C=N vibrational bands. The mass spectra of the 1,3,4-oxadiazoles XVII-XIX showed molecular ion peaks at m/e 253, 267 and 287 (289 for M + 2) respectively. In accordance with the ions produced under electron impact, the fragmentation of these compounds was generally found to follow the general fragmentation pattern anticipated for oxadiazoles [27-30]. The base peaks appeared at m/e 93, 92 and 127 for the phenyl- (XVII), *m*-tolyl- (XVIII) and *p*-chlorophenyl- (XIX) 1,3,4-oxadiazoles respectively.

The products were screened for anticonvulsant properties by determining the elevation of the convulsant threshhold to the intravenous infusion of metrazol to mice. The tests were performed in accordance with the protocol of biological screening program, Beecham pharmaceuticals, U. K. No anticonvulsant activity was exhibited by any of the products.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The ir spectra were recorded as nujol mulls on a Beckman 4210 ir spectrophotometer. The ^{1}H nmr spectra were measured on a Varian EM 360L and the ms on a Finnigan 3200.

1-(3',5'-Dibromo)salicyl-4-aryl-3-thiosemicarbazides (XII-XVI). General Procedure.

To a solution of 3,5-dibromosalicylhydrazide (III) [19] (1.5 g, 4.8 mmoles) in 30 ml of ethanol at room temperature was added the equivalent amount of the appropriate arylisothiocyanates in 5 ml of ethanol. The clear solution was heated under reflux for 30 minutes, partially concentrated and allowed to cool to room temperature to deposit the phenyl- (XII) and *p*-tolyl- (XIII) thiosemicarbazides. In the case of *p*-methoxyphenyl- (XIV), *p*-chlorophenyl- (XV) and *p*-bromophenyl- (XVI) thiosemicarbazides, the products separated during the reflux period and the yield increased on cooling to room temperature. The products were filtered, washed with light petroleum and crystallized from ethanol or a mixture of the ethanol and acetone. The yield and physical constants of the products are recorded in Table I. The ir and ^{1}H-nmr spectra were consistent with the structure of the thio functions [31].

2-Substituted Amino-5-aryl-1,3,4-oxadiazoles (XVII-XXVIII). General Procedure.

Method A. Cyclodesulfurization With DCCD.

To a solution of the thiosemicarbazides V-XVI (700 mg) in 50 ml of benzene or a mixture of 50 ml of benzene and 2 ml of acetone at room temperature was added 1.5 molar equivalents of DCCD. The mixture was heated under reflux for 6 hours, partially concentrated and allowed to cool to room temperature to deposit the 2-arylamino-5-aryl-1,3,4-oxadiazoles. These were filtered and crystallized from a mixture of benzene and acetone as white crystals identified as shown in Table II. In the case of 2-benzylamino- (XXI), 2-butylamino- (XXII) and 2-cyclohexylamino- (XXIII) 1,3,4-oxadiazoles, the final reaction mixture was concentrated, allowed to cool to room temperature and the clear solution was treated with a saturated solution of picric acid in ethanol. The picrate salts were filtered, crystallizied from aqueous ethanol and identified as specified in Table II.

Method B. Cyclodesulfurization With Mercuric Oxide.

A mixture of the thiosemicarbazides V-XVI (300 mg) and freshly precipitated mercuric oxide (4 molar equivalents) in 30 ml of ethanol was heated under reflux for 4 hours. The mixture was allowed to cool to room temperature to allow the sedimentation of the black mercuric sulfide, filtered and mercuric sulfide was washed with ethanol. The filtrate and alcoholic washings were combined, partially evaporated, treated with water until a permanent turbidity existed and allowed to stand overnight. The products were then separated and identified as mentioned in Table II; ms: m/e (relative abundance %) compound XVII, 253 (70) ($M^{+\cdot}$), 236 (2), 211 (5), 197 (7), 196 (21), 180 (2), 167 (2), 161 (43), 135 (3), 134 (12), 133 (18), 121 (93), 105 (70), 93 (100); compound XVIII, 267 (65) ($M^{+\cdot}$), 250 (3), 241 (5), 240 (51), 255 (6), 211 (2), 210 (22), 196 (4), 162 (1), 161 (42), 159 (17), 148 (28), 134 (4), 133 (37), 131 (6), 121 (91), 118 (40), 116 (7), 107 (94), 105 (44), 102 (3), 94 (2), 93 (20), 92 (100), 91 (61), 89 (2), 85 (2), 84 (3), 83 (51); compound XIX, 289 (23) (M + 2), 287 (39) ($M^{+\cdot}$), 233 (1), 232 (3), 231 (5), 230 (11), 168 (1), 167 (2), 161 (70), 154 (3), 152 (3), 141 (1), 140 (2), 139 (2), 138 (5), 133 (23), 130 (1), 129 (18), 127 (100), 121 (46), 119 (73), 106 (7), 105 (45), 102 (7), 94 (2), 93 (37), 91 (84), 88 (2), 85 (6).

One-pot Cyclodesulfurization of Mixtures of the Salicylhydrazides V and XII and Phenylisothiocyanate With DCCD.

To a solution of the salicylhydrazides V and XII (200 mg) in 30 ml of hot benzene was added a solution of the equivalent amount of phenylisothiocyanate in 5 ml of benzene and the mixture was heated under reflux for 30 minutes. Two ml of acetone was added to dissolve the precipitate which formed followed by addition of 330 mg of DCCD. The mixture was heated under reflux for an additional 6 hours and the clear solution was concentrated, allowed to cool to room temperature to give the cyclized products XVII and XXIV in 66 and 70% yield respectively after crystallization from a mixture of benzene and ethanol.

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