N-Substituted 4,5-Dihydro-1,2-benzothiazepin-3-one 1,1-Dioxide

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The reaction of 2-carboethoxyethyl-4,5-dimethoxybenzene sulfochloride with substituted pyridines leads to the corresponding sulfonamides. The latter were hydrolysed to the acids, on which a general method for preparing a new ring system was based.

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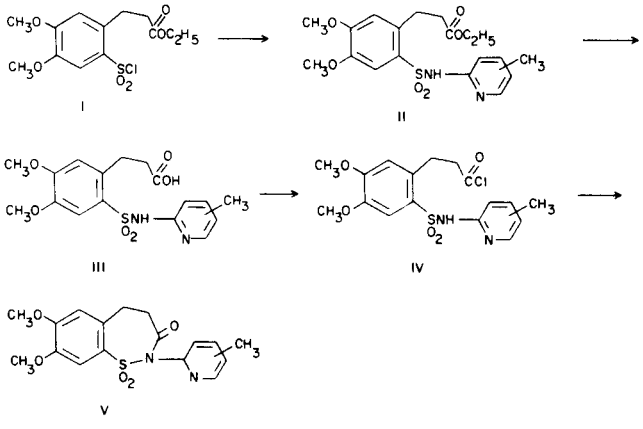
In a previous communication (1) we have reported the synthesis and pharmacological properties of 6,7-dimethoxy-2-(2-pyridyl)benzo-1,2-thiazin(4*H*)-3-one 1,1-dioxides.

In conjunction with our investigation of the thia-azo heterocyclic compounds (2-4) we thought it would be of interest to extend this work to the synthesis of *N*-pyridyl-4,5-dihydro-1,2-benzothiazepin-3-one 1,1-dioxides, since related structure compounds indicated interesting pharmacological properties (6-9).

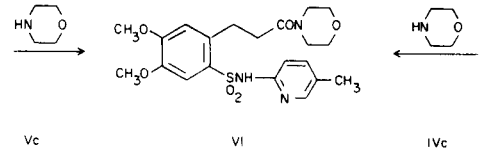
Starting from the 2-carboethoxyethyl-4,5-dimethoxybenzenesulfochloride (5) and substituted aminopyridines we obtained compound II in good yield.

By the hydrolysis of the esters which was followed by treatment with phosphorus pentachloride, the acid-chlorides IV were obtained, which were heated in xylene to give the benzothiazepinones V.



Treatment of Vc with sodium hydroxide, followed by acidification gave the free acid IIIc.

Further confirmation of the benzothiazepinone structure was achieved by the following chemical transformations. Treatment of Vc with morpholine 4,5-dimethoxy-2-morpholinocarboxamidoethylbenzene-*N*-(2-pyridyl)sulfonamide was obtained. The structure of VI was confirmed by its independent synthesis from 4,5-dimethoxychlorocarboxyethylbenzene-*N*-(2-pyridyl)sulfonamide and morpholine.



EXPERIMENTAL

Preparation of the *N*-Substituted Sulfonamides (II).

To a solution of 3 mmoles of I in 25 ml. of anhydrous benzene, 6 mmoles of aminopyridine was added and the mixture was refluxed for 3 hours. The solvent was evaporated and ice-water was added to yield the corresponding sulfonamides in solid form. All of the ester-sulfonamides obtained showed strong absorption at 3230 (NH), 1715 cm^{-1} (C=O).

The compounds prepared are summarized in Table I.

Preparation of the *N*-Substituted 2-Carboxyethyl-4,5-dimethoxybenzenesulfonamides (III).

To a solution of 50% aqueous methanol containing 1 g. of potassium hydroxide, 1 g. of ester II was added and the mixture was refluxed for 3

Table I

2-Carboethoxyethyl-4,5-dimethoxybenzene-(2-methylpyridyl)sulfonamides

Compound	M.p. °C (Recrystallized from)	Yield	Formula	Calcd. % / Found % C	H	N
IIa, 3-CH_3	116-118 (CH_3OH)	56	$C_{19}H_{24}N_2O_6S$	55.88	5.88	6.86
				55.98	5.97	6.88
IIb, 4-CH_3	197-199 (CH_3OH-$CHCl_3$)	76	$C_{19}H_{24}N_2O_6S$	55.88	5.88	6.86
				55.48	5.74	6.69
IIc, 5-CH_3	161-162 (CH_3OH-$CHCl_3$)	82	$C_{19}H_{24}N_2O_6S$	55.88	5.88	6.86
				55.37	5.49	6.50

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Table II

2-Carboxyethyl-4,5-dimethoxybenzene-(2-methylpyridyl)sulfonamides

Compound	M.p. °C (Recrystallized from)	Yield	Formula	Calcd. % Found % C	H	N
IIIa, 3-CH_3	161-162 (CH_3OH)	34	$C_{17}H_{20}N_2O_6S$	53.68	5.26	7.36
				53.28	5.52	6.98
IIIb, 4-CH_3	259-260 (CH_3OH-$CHCl_3$)	77	$C_{17}H_{20}N_2O_6S$	53.68	5.26	7.36
				53.64	5.29	7.42
IIIc, 5-CH_3	250-252 (CH_3OH-$CHCl_3$)	86	$C_{17}H_{20}N_2O_6S$	53.68	5.26	7.36
				53.90	5.05	7.30

Table III

N-Pyridyl-4,5-dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one-1,1-dioxides

Compound	M.p. °C (Recrystallized from)	Yield	Formula	Calcd. % Found % C	H	N
Va, 3-CH_3	188-190 (CH_3OH)	42	$C_{17}H_{18}N_2O_5S$	56.35	4.97	7.53
				56.12	4.69	7.58
Vc, 5-CH_3	176-178 (CH_3OH)	71	$C_{17}H_{18}N_2O_5S$	56.35	4.97	7.53
				55.98	4.89	7.47

hours. The solution was poured into ice-water and acidified with acetic acid. The reaction mixture was extracted with chloroform. The organic layer was washed with water and dried over magnesium sulfate. After evaporation of the solvent the residue was crystallized from the appropriate solvent; ν max 1700 cm^{-1} (C=O).

The compounds prepared are reported in Table II.

Preparation of the *N*-Substituted-4,5-dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one 1,1-Dioxides (V).

To a flask containing III (1 g.) in 30-50 ml. of anhydrous benzene was added 2 g. of phosphorus pentachloride and the mixture was agitated at room temperature for 72 hours. The resulting precipitate was filtered and washed with anhydrous benzene and dried over phosphorus pentoxide.

All the acid chlorides obtained showed strong absorption at 1725 cm^{-1} (C=O).

Three hundred mg. of the above prepared acid chloride was added to 10 ml. of anhydrous xylene and heated under reflux for 20 hours. After this time the solvent was evaporated under reduced pressure and the residue was dissolved in water and neutralized with ammonia. The precipitate was collected by filtration and crystallized from the appropriate solvent; ν max 1700 cm^{-1} (C=O).

The compounds prepared are summarized in Table III.

Hydrolysis of Vc.

To a solution of 30% methanol (20 ml.) containing 100 mg. of potassium hydroxide, 100 mg. of Vc was added and the mixture was stirred at room temperature for 5 hours. The solution was poured into ice-water and acidified with dilute hydrochloric acid. The resulting precipitate was collected by filtration to yield compound IIIc quantitatively which was identical by comparison of its melting point and infrared spectrum to the authentic compound.

4,5-Dimethoxy-2-morpholinocarboxamidoethylbenzene-*N*-[2-(5-methylpyridyl)]sulfonamide (VI).

Method A.

A solution of 100 mg. of dihydrodibenzothiazepinone (Vc) in 3 ml. of anhydrous toluene and 2 ml. of morpholine was refluxed for 24 hours. The solvent with the excess amine was evaporated under reduced pressure and the residue was crystallized from chloroform ethanol to give VI (80 mg.), m.p. 206°.

Anal. Calcd. for $C_{21}H_{27}N_3O_6S$: C, 56.12; H, 6.01; N, 9.35. Found: C, 56.03; H, 6.19; N, 9.20.

Method B. From 4,5-Dimethoxychlorocarboxyethylbenzene-*N*-[2-(5-methylpyridyl)]sulfonamide.

To a flask containing 100 mg. of acid chloride, an excess of morpholine (12 ml.) was added and the reaction mixture was heated on a steam bath for 2 hours. The excess amine was evaporated under reduced pressure and water was added to yield a solution which was extracted with chloroform. The organic layer was washed with water and dried over magnesium sulfate. Removal of the solvent produced a residue which was crystallized from chloroform-ethanol to give VI, identical by comparison of melting point and infrared spectrum to the compound prepared by Method A.

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