Notes

Chem. Pharm. Bull. 29(8)2359—2361(1981)

Syntheses of 2-Sulfamoylmethylbenzoxazole Derivatives and Determination of Their Anticonvulsant Activities

Hitoshi Uno,* Mikio Kurokawa and Yoshinobu Masuda

Research Laboratories, Dainippon Pharmaceutical Co., Ltd. 33-94, Enokicho, Suita, Osaka 564, Japan
Research Laboratories, Dainippon Pharmaceutical Co., Ltd.

(Received February 16, 1981)

Some 2-sulfamoylmethylbenzoxazole derivatives were synthesized from 2-bromomethylbenzoxazole by reaction with sodium bisulfite, followd by chlorination and amination. Among them, 2-sulfamoylmethylbenzoxazole (**5a**) showed the strongest anticonvulsant activity, which was compared with that of 3-sulfamoylmethyl-1,2-benzisoxazole (I).[1]

Keywords——2-sulfamoylmethylbenzoxazole; anticonvulsant activity; bromination; sulfonation; maximal electroshock seizure

In the previous paper,[1] it was shown that 3-sulfamoylmethyl-1,2-benzisoxazole (I) exerted a potent anticonvulsant effect as measured in terms of protection against maximal electroshock seizure (MES). As a continuation of this work, some 2-sulfamoylmethylbenzoxazole derivatives were synthesized and their biological activities were evaluated.

The bromination of 2-methylbenzoxazole (**1**) with N-bromosuccinimide (NBS) afforded 2-bromomethylbenzoxazole[2] (**2**). The treatment of **2** with sodium sulfite gave sodium benzoxazole-2-methanesulfonate (**3**). The chlorination of **3** with phosphorus oxychloride gave benzoxazolemethanesulfonyl chloride (**4**), which was converted to 2-sulfamoylmethylbenzoxazole (**5a**) by treatment with ammonia and to several N-substituted derivatives (**5b—d**) of **5a** by treatment with appropriate amines.

Starting from 5-chloro-2-methylbenzoxazole (**6**), the 5-chloroderivative (**5e**) of **5a** was obtained *via* the same processes.

Protection against MES was determined according to the method of Swinyard[3] using mice. ED_{50} values, summarized in the table, indicated marked activities against MES following administration of all compounds. Among them, **5a** was the most potent compound and its activity was comparable to that of I.[1] The introduction of a halogen atom at the 5 position of **I** increased the potency. However, the introduction of a chlorine atom at the 5 position

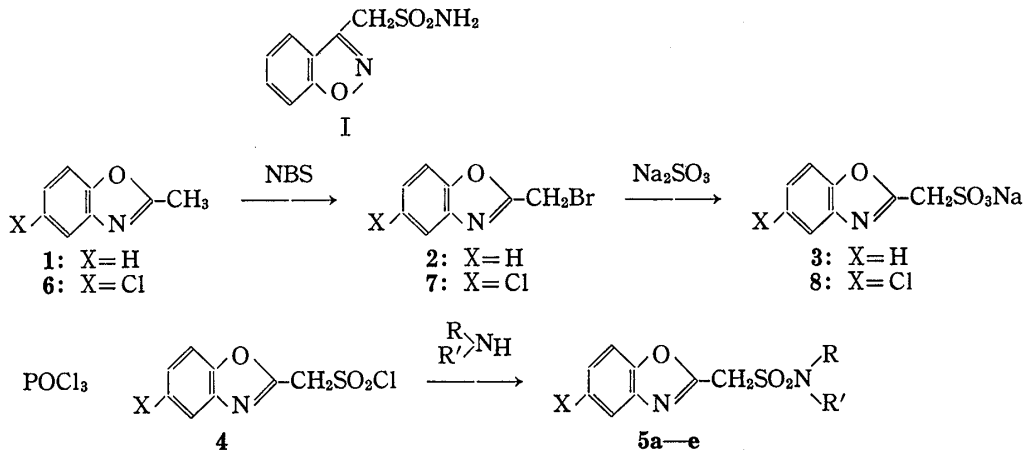
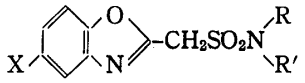


Chart 1

TABLE I. Melting Points, Yields, Formulae, Microanalytic Data and Anticonvulsant Activities of 2-Sulfamoylmethylbenzoxazoles (**5**)



No.	X	$N\langle^{R}_{R'}$	mp °C[a]	Yield[b] (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Anti-MES; ED_{50} mg/kg, *p.o.*
5a	H	NH_2	166—169	8	$C_8H_8N_2O_3S$	45.27 (45.17	3.80 3.56	13.20 13.12	15.11 15.29)	12.0 (7.2—17.5)[d]
5b	H	$NHCH_3$	139—142	8.2	$C_9H_{10}N_2O_3S$	47.76 (47.76	4.46 4.38	12.38 12.55	14.17 14.17)	17.2 (10.5—26.9)
5c	H	$N(CH_3)_2$	109—111	6.7	$C_{10}H_{12}N_2O_3S$	49.98 (50.02	5.04 5.31	11.66 11.89	13.35 13.42)	34.0 (18.1—56.2)
5d	H	NH(*n*-Pr)	146—149	5.2	$C_{11}H_{14}N_2O_3S$	51.95 (52.09	5.55 5.45	11.02 11.12	12.61 12.40)	31.2 (13.2—49.7)
5e	Cl	NH_2	188—191	29.5	$C_8H_7ClN_2O_3S$[c]	38.95 (38.97	2.86 3.02	11.36 11.50	13.00 12.93)	30.3 (22.2—41.4)
Diphenylhydrantoin										10.0 (7.6—12.3)

a) Recrystallized from AcOEt.
b) Yields were calculated from 2-methylbenzoxazoles.
c) Cl; Calcd. 14.37. Found. 14.13.
d) 95% confidence limits.

of the benzoxazole ring (**5e**) caused a slight decrease in the potency. The replacement of the amino group with a simple alkyl group also caused a decrease of the activity, and the order of decreasing potency for the alkylated derivatives of this series was in good agreement with that obtained in the series of 1,2-benzisoxazole derivatives.[1] Therefore, it is possible that the potency of these compounds might be the result of biotransformation, as suggested by Smith *et al.*[4]

Compound **5a** showed very low toxicity in animals[5] and was considered to be the most promising compound as an anticonvulsant.

Experimental

All melting points are uncorrected. PMR spectra were taken with a Varian 100 spectrometer using TMS as an internal standard.

2-Bromomethylbenzoxazole[2] (**2**)——A solution of 2-methylbenzoxazole (**1**) (35 g, 0.263 mol) in CCl_4 (300 ml) was treated with NBS (47 g, 0.263 mol) and benzoyl peroxide (1.0 g). The mixture was refluxed for 90 h then cooled. Succinimide was filtered off and the mixture was evaporated to dryness. The residual oil was subjected to chromatography on silica gel. The fraction eluted with toluene was collected and evaporated to dryness to give 16 g (28%) of crude **2**. PMR (in $CDCl_3$) δ: 4.34 (2H, s, $-C\underline{H}_2-$). This product was used in the next process without any purification.

From the fraction eluted with $CHCl_3$, 8 g (23%) of **1** was recovered.

2-Bromomethyl-5-chlorobenzoxazole (**7**)——The bromination of 2-methyl-5-chlorobenzoxazole(**6**) (40 g) with NBS (47 g) and benzoyl peroxids (1.0 g) in CCl_4 (440 ml) for 100 h at 90°C gave **7** (29 g, 59%) as an oil.

Sodium benzoxazole-2-methanesulfonate (**3**)——A solution of **2** (16 g) in MeOH (200 ml) was treated with a solution of Na_2SO_3 (10.4 g) in H_2O (200 ml) and the mixture was stirred at 40°C for 16 h. The solvent was removed and the residue was well dried. Crude **3** (24 g) thus obtained was used in the next process without any purification.

5-Chloro Derivative of 3 (**8**)——Crude **8** (1.74 g) was obtained from **7** (1.0 g) by the same procedure as described above.

2-Sulfamoylmethylbenzoxazole (**5a**)——The crude **3** (4.5 g) was dissolved in $POCl_3$ (15 ml) and the solution was refluxed for 30 min. Excess $POCl_3$ was removed and the residue was dissolved in AcOEt (100 ml). The solution was saturated with dry ammonia under cooling. After 30 min, the solvent was removed

and the residual oil was chromatographed on silica gel. The fraction eluted with 3% MeOH–$CHCl_3$ was evaporated to dryness and the residue was recrystallized from AcOEt to give 0.25 g of **5a**.

Preparations of 5b—e——Compounds 3 (4.5 g) was chlorinated with $POCl_3$. The sulfonylchloride was dissolved in AcOEt (100 ml). The solution was treated with $MeNH_2$ (saturation), Me_2NH (saturation) and propylamine (20 ml) to give **5b** (1.4 g), **5c** (0.6 g) and **5d** (0.85 g), respectively.

Compound **5e** (0.5 g) was obtained from **8** (1.74 g) by the method described above.

Melting points, yields and the results of elemental analyses are given in the table.

Anticonvulsant Activity——All experiments were carried out in male mice of STD-ddr strain weighing 20—22 g. Diet and water were given *ad libitum* to animals until the time of experiment. All compounds were administered by gavage as a suspension of 0.5% tragacanth solution. Drugs were evaluated for ability to prevent the hindlimb tonic extensor component of MES induced by a 60-Hz, 25 mA current for 0.2 s, delivered through corneal electrodes 2 h after dosing. DE_{50} values were calulated by the method of Litchfield and Wilcoxon.[6]

Acknowledgment We are grateful to Dr. H. Nishimura, the director of these laboratories, for his encouragement throughout of this work and to Dr. T. Karasawa for helpful discussions.

References and Notes

1) H. Uno, M. Kurokawa, Y. Masuda, and H. Nishimura, *J. Med. Chem.*, **22**, 180 (1979).
2) F. Dersch and M. R. De Angeles, Belg. Patent 624463 (1963) [*C.A.*, **59**, P2318*g* (1963)].
3) E.A. Swinyard, *J. Am. Pharm. Assoc., Sci. Ed.*, **38**, 201 (1963).
4) D.L. Smith, H.H. Keasling, and A.A. Forist, *J. Med. Chem.*, **8**, 520 (1965).
5) H. Uno, M. Kurokawa, and Y. Masuda, Japan Kokai 79-163, 570 (1979) [*C.A.*, **93**, P95260*s* (1980)].
6) J.T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

[Chem. Pharm. Bull. 29(8)2361—2366(1981)]

Ring Transformation of 5-Oxo-4-oxaspiro[2.3]hexanes

TETSUZO KATO,* NOBUYA KATAGIRI, and RENZO SATO

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(Received March 2, 1981)

1-Ethoxycarbonyl-5-oxo-4-oxaspiro[2.3]hexane (**3**), on treatment with sodio methyl acetoacetate in THF, was transformed into 3-hydroxy-4-ethoxycarbonyl-2-cyclopenten-1-one (**5**) in 82% yield. Reaction of compound **3** with malononitrile (**4a**) in the presence of sodium hydride in THF gave the cyclopentenone **5** and 2-amino-3-cyano-6-ethoxycarbonylethyl-4-pyrone (**6**) in 49% and 24% yields, respectively. Similarly, reaction of compound **3** with ethyl cyanoacetate (**4b**) afforded compound **5** and 2-amino-3-ethoxycarbonyl-6-(2-ethoxycarbonylethyl)-4-pyrone (**7**) in 63% and 19% yields, respectively.

Reaction of 1-dimethylphosphono-1-methyl-5-oxo-4-oxaspiro[2.3]hexane (**1c**) with **4a** and **4b** under similar conditions gave 2-amino-3-cyano-6-(2-dimethylphosphonopropyl)-4-pyrone (**10**) and 2-amino-3-ethoxycarbonyl-6-(2-dimethylphosphonopropyl)-4-pyrone (**11**) in 58% and 63% yields, respectively.

Keywords——ring transformation; 5-oxo-4-oxaspiro[2.3]hexanes; active methylene compounds; 2-cyclopentenones; 2-amino-4-pyrones

During the course of investigations of the addition reaction of carbenes to the oxo double bond of diketene to give 5-oxo-4-oxaspiro[2.3]hexanes,[1–4] we have observed a novel ring transformation of 1-aryl-1-dimethylphosphono-5-oxo-4-oxaspiro[2.3]hexanes (**1a, b**) prepared from diketene and dimethyl (diazoarylmethyl)phosphonate, on treatment with methyl acetoacetate in the presence of sodium hydride, to 4-aryl-4-dimethylphosphono-3-hydroxy-2-cyclo-