OXYGEN-CONTAINING HETEROCYCLES.*

XVII. SYNTHESIS AND ANTICONVULSANT ACTIVITY OF CYCLIC 1,3-BENZODIOXOLE-2-CARBOXY-2-ACETIC IMIDES AND AMINES

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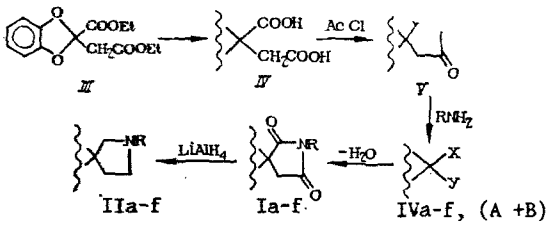
UDC 615.213:547.852.9].012.1

Many known derivatives of 1,3-benzodioxole have a broad spectrum of biological activity [6, 7]. Spiro(1,3-benzodioxole-2,3'-pyrrolidine) and its N-methyl- and benzyl derivatives have been described in the literature [4, 8]. However, information about its action on the CNS is given only for the nonsubstituted product.

In order to establish the connection between the structure of this series of compounds and their biological activity, we synthesized N-substituted imides of 1,3-benzodioxole-2-carboxy-2-acetic acid (Ia-f) and N-substituted derivatives of spiro(1,3-benzodioxole-2,3'-pyrrolidine (IIa-f).



I, II, VI: R = H(a), Me(b), Et(c), Pr-*i*(d), Bu(e), CH_2Ph(f); VIA:X=CONHR, $Y = CH_2COOH$; VIB:X = COOH, $Y = CH_2CONHR$.

Our proposed method of synthesizing compounds I and II was accomplished through the cyclic anhydride of 1,3-benzodioxole-2-carboxy-2-acetic acid (V) which has not been described in the literature. In the course of the synthesis we also identified unfamiliar amido acids (VI) which might be of interest in themselves for the synthesis of biologically active substances of the benzodioxole series.

Diethyl 1,3-benzodioxole-2-carboxy-2-acetate (III) and the corresponding diacid (IV) were used as the starting substances fo the synthesis of I and II. The anhydride of diacid IV was obtained by heating with a fivefold quantity of AcCl. The reaction between the anhydride and various primary amines led to the formation of a mixture of amido acids with a structure like that of VIA and B. One of each compound was formed along an elongated spot on Silufol UV-240 plates and silica gel (fixed layer) in various mobile phases.

Amides I were obtained by further cyclization of the amido acids at 200°C.

The next stage was the reduction of the imides of I by lithium aluminum hydride which was accompanied by a partial cleavage of the benzodioxole ring to a pyrocatechol [8] which in turn explains the low yield of the target products. Along with catechol, the cleavage of the If imide resulted in the formation of N-benzylpyrrolidine whose structure was proved by physico-chemical methods.

The IR spectra of the I imides have absorption bands in the 1720-1740 cm^{-1} region (broad band) which are characteristic of the carbonyl groups. These absorption bands are

*See [1] for previous communication.

A. L. Mndzhiyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimikofarmatsevticheskii Zhurnal, Vol. 21, No. 1, pp. 34-37, January, 1987. Original article submitted July 22, 1985.

 0091-150X/87/2101-0030$12.50

absent in the IR spectra of the benzodioxolopyrrolidines of compound II. The PMR spectra of the II compounds exhibit proton signals of the pyrrolidine ring in the 2.2-3.0 ppm region. Molecular ion and characteristic fragment peaks were found in the mass spectra of the synthesized compounds.

EXPERIMENTAL – CHEMICAL

Chromatography of the synthesized compounds was performed on Silufol UV-254 plates. Iodine vapor was used as the developer. IR spectra were recorded on a UR-20 instrument in petroleum jelly. Mass spectra were recorded on an MX-1303 instrument with direct sample injection into the ion source. PMR spectra were recorded on a Varian (60 MHz) instrument. Melting point was determined on a micro-hot plate.

Diethyl 1,3-benzodioxole-2-carboxy-2-acetate (III) was synthesized by the method described in [1].

1,3-Benzodioxole-2-carboxy-2-acetic acid (IV) was obtained with yield of 82% and a mp of 179-180°C (mp 177-179°C, according to the literature [8]).

Anhydride of 1,3-benzodioxole-2-carboxy-2-acetic Acid (V). A 39.25-g portion (0.5 mole) of AcCl was added to 22.4 g (0.1 mole) of diacid IV and the mixture was heated for 2-3 h. The excess AcCl and AcOH was then distilled off, and 100 ml of abs. ether were added to the oily residue. The resultant crystals were recrystallized from abs. ether. Yield of V was 12.4 g (60%). mp 201-202°C. Found, %: C 58.30; H 2.50. $C_{10}H_6O_5$. Calculated, %: C 58.03; H 2.91. R_f 0.51 (ethyl acetate–ester, 7:1). IR spectrum, νmax, cm^{-1}: 1740, 1810 (C=O anhydride).

Amido Acids A (VIa) and B (VIa) (Isomer Mixture). A 1.7-g (0.1 mole) portion of ammonia in 50 ml of ethyl acetate was slowly added to a solution of 10.8 g (0.05 mole) of anhydride V in 100 ml of ethyl acetate. The reaction was then left for 2-3 h at 20-25°C. The precipitated crystals were filtered off, the filtrate was washed with water. The aqueous solution was added to the crystals and the solution was acidified with diluted HCl (1:1) to the acid point, followed by extraction with ether. The solution was dried with Na_2SO_4, the solvent was distilled off, and the residue was recrystallized from acetone (Table 1). IR spectra, νmax, cm^{-1} 3200-3600 (NH, OH), 1720 (C=O acid), 1655 (C=O amide).

Amido Acids VIb-e. These acids were obtained in the same way as the VIa acids, with the use of alkylamines instead of ammonia (see Table 1).

1,3-Benzodioxole-2-carboxy-2-acetic Imide (Ia). Amido acid IVa was heated on a Wood's bath at 200°C until all the water was liberated. The oily product was then redistilled in a vacuum (Table 2). PMR spectrum, δ, ppm.: 6.8 singlet (4H, H aromatic), 3.2 singlet (2H, CH_2C=O), 2.13 singlet (1H, NH). M^+ 205 (mass spectrometrically).

TABLE 1. Amido Acids VI (A + B)

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			R_f^*
			C	H	N		C	H	N	
VIa	76,9	165—6	53,67	4,21	6,38	$C_{10}H_9NO_5$	53,81	4,06	6,27	0,40
VIb	88,8	89—90	55,91	4,73	5,68	$C_{11}H_{11}NO_5$	55,70	4,67	5,90	0,43
VIc	82,9	101—2	57,45	5,08	5,39	$C_{12}H_{13}NO_5$	57,37	5,21	5,57	0,51
VId	70,3	167—8	58,92	5,48	5,34	$C_{13}H_{15}NO_5$	58,85	5,69	5,27	0,47
VIe	70,4	145—6	59,80	6,08	4,98	$C_{14}H_{17}NO_5$	60,03	6,13	5,01	0,50

*Phenol–cresol–HCOOH (3:7:1), developer bromocresol blue (silica gel)

TABLE 2. N-Substituted Imides of 1,3-Benzodioxole-2-carboxy-2-acetic Acid Ia-f

Compound	Yield, %	mp, °C	bp, °C/mm Hg	Found, %			Empirical formula	Calculated, %			R_f^a
				C	H	N		C	H	N	
Ia	72,7	159—60b	209—10/2	58,61	3,72	6,90	$C_{10}H_7NO_4$	58,54	3,44	6,82	0,35
Ib	75,0	106—8	175—80/2	60,6	4,10	6,49	$C_{11}H_9NO_4$	60,45	4,13	6,38	0,55
Ic	73,4	102—3	190—5/2	62,10	4,40	5,59	$C_{12}H_{11}NO_4$	62,22	4,75	6,00	0,63
Id	85,0	122—3	200—5/2	63,30	5,54	5,88	$C_{13}H_{13}NO_4$	63,16	5,30	5,66	0,44
Ie	86,4	75—6	225—30/2	64,26	5,62	4,99	$C_{14}H_{15}NO_4$	64,36	5,78	5,36	0,53
If	72,1	139—40c	250—2/1	68,77	4,09	4,08	$C_{17}H_{13}NO_4$	69,22	4,43	4,07	0,63

[a]Ether—Chloroform, 4:1
[b]mp 160—161°C, according to [8]
[c]mp 138—139°C, according to [4]

N-substituted imides Ib-e were obtained in the same way as Ia (see Table 2).

1,3-Benzodioxole-2-carboxy-2-acetic n-benzylimide (If) was obtained by the method in [4] with a yield of 71%, mp 139—140°C (136—138°C according to the literature data).

N-Butylspiro(1,3-benzodioxole-2,3'-pyrrolidine) (IIe). A 4.2-g (0.02 mole) portion of Ie imide in 50 ml of abs. ether was added dropwise to 3.12 g (0.08 mole) of $LiAlH_4$ in 100 ml of abs. ether and heated for 16-18 h. After the mixture was cooled, 20 ml of water were added. The resultant precipitate was filtered off, washed with ether, and the filtrate was dried by Na_2SO_4. The solvent was distilled off, and the residue was redistilled in a vacuum (Table 3). PMR spectrum, δ, ppm.: 6.68 singlet (4H, H aromatic), 2.9 singlet (2H, CH_2), 2.8—2.15 multiplet [6H, $CH_2N(CH_2)_2$], 1.6-1.2 multiplet (4H, CH_2CH_2), 1.18-0.85 triplet (3H, CH_3).

N-substituted spiro(1,3-benzodioxol-2,3'-pyrrolidines) IIa-d, f were obtained in the same way as IIe (see Table 3).

EXPERIMENTAL—PHARMACOLOGICAL

The anticonvulsant activity of the Ia-f imides and the pyrrolidine IIa-f hydrochlorides was examined. The tests were conducted on 220 white mice weighing 18-24 g. Maximum electric shocks [10], antagonism with corazole [9], nicotine [3], and arecoline [2] were used as the convulsant models. The daily acute toxicity in the mice was also determined. The test compounds were administrated intraperitoneally 20 min prior to the administration of the convulsants and the application of an electric current across corneal electrodes. A total of 12 compounds were examined, of which six were imides and six were reduced analogs.

The test results demonstrated that none of the examined compounds, regardless of structure, attenuated nicotine convulsions or arecoline tremor, i.e., non of them exhibited central H- and M-cholinolytic action. Furthermore, none of the compounds exhibited anti-corazole activity. The Ia-f imides were less active than the reduced analogs with respect to electrically induced convulsions. The latter compounds prevented electric stimulation to one degree or another, i.e., they protected the animals against tonic extension of maximum electric shock.

Comparative experiments were conducted with recognized anticonvulsants from the succimide group, such as Milontin which is used for the treatment of epilepsy.

The Litchfield and Wilcoxon probit analysis method [5] was used to determine the average effective doses (ED_{50}) and for a comparative quantitative evaluation of the compounds' anticonvulsant activity. The same method was used to determine the average lethal doses (LD_{50}). The greatest degree of activity was manifested by compounds IId and IIe with isopropyl and butyl radicals at a dose of 200 mg/kg. Table 4 shows the comparative characteristics of their anticonvulsant activity in the maximum electric shock test.

As can be seen from Table 4, compounds IId and IIe approach Milontin in ability to prevent the tonic extension phase of electric shock, although they are more toxic.

TABLE 3. N-Substituted Spiro-(1,3-benzodioxol-2,3'-pyrrolidine) IIa-f

Compound	Yield, %	mp of the hydrochloride, °C	bp, °C/mm Hg	Found %			Empirical formula	Calculated, %			n_D^{20}	R_f^a
				C	H	N		C	H	N		
IIa	38,1	240—2 [b]	115—6/1	67,40	6,35	7,53	$C_{10}H_{11}NO_2$	67,21	6,25	7,88	1,5329	0,60
IIb	55,8	137—8 [c]	125—6/1	69,21	6,70	7,52	$C_{11}H_{13}NO_2$	69,10	6,85	7,32	1,5058	0,50
IIc	42,3	164—5	134—5/1	70,10	7,28	6,62	$C_{12}H_{15}NO_2$	70,23	7,36	6,82	1,5222	0,43
IId	54,2	134—5	155—6/1	71,18	8,10	6,19	$C_{13}H_{17}NO_2$	71,20	7,81	6,38	1,5100	0,52
IIe	53,2	95—6	160—1/1	72,10	7,88	6,37	$C_{14}H_{19}NO_2$	72,09	8,20	6,00	1,5150	0,66
IIf	66,2	127—8	170—3/2	76,38	6,41	5,20	$C_{17}H_{17}NO_2$	76,00	6,50	5,02	—	0,67

[a] Butanol—AcOH—water, 5:3:3
[b] mp 245—246°C, according to [4]
[c] mp of oxalate
[d] bp 159—163/0.25 mm Hg, according to [4]
(not indicated in Russian original — publisher)

TABLE 4. Anticonvulsant Activity and Toxicity of IId and IIe Hydrochlorides

Compound	ED_{50}, mg/kg	LD_{50}, mg/kg	LD_{50}/ED
IId	120 (98,3—146,4)	350 (315,3—388,5)	2,9
IIe	74 (39,2—92,5)	310 (254,1—378,2)	4,2
Milontin	64 (47,4—86,4)	950 (720—1140)	14,0

Thus, in spite of our expectations, compounds I, whose structures are similar to those of the succinimides, did not exhibit any marked anticonvulsant activity whereas their reduced analogs did exhibit some selective anticonvulsant action in electric shock.

Compounds Ia-f do not exhibit any antiarrythmic action, but compounds IIa-f did exhibit slight adreno- and sympatholytic activity.

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