Synthesis and Anticonvulsant Activity of 1-Aryl-3-methylene-2-pyrrolidinone Adducts

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Reaction of 1-aryl-3-methylene-2-pyrrolidinones with several active hydrogen compounds resulted in a Michael addition to give the title compounds. The compounds were screened in the maximal electroshock seizure and subcutaneous pentylenetetrazol seizure threshold tests for anticonvulsant activity and in the rotorod test for neurotoxicity in mice. Several compounds displayed anticonvulsant activity, but only at the high dose levels of 300 or 600 mg/kg.

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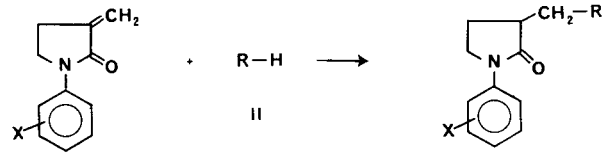
Routine screening of several 1-aryl-3-methylene-2-pyrrolidinones for anticonvulsant activity revealed that one of the compounds (Ia, X = *p*-CH_3) possessed activity with no toxicity at 300 mg/kg when evaluated in the subcutaneous pentylenetetrazole seizure threshold test in mice. These compounds were available from another study [1] and were tested since other workers have found 2-pyrrolidinones possessing anticonvulsant activity [2]. The low order of activity of compounds I may be due to their propensity to react with biological nucleophiles thus preventing them from reaching the site of action. Adducts of I (compounds III) on the other hand, would be free from such a shortcoming, and once at the site of action could revert to I by loss of the active hydrogen addend (II) (Scheme I). Furthermore, compounds III may themselves possess anticonvulsant activity. This report is concerned with the synthesis and anticonvulsant testing of a series of 1-aryl-3-methylene-2-pyrrolidinone adducts III.

Scheme I



I II III

The addends chosen for this study included methanol, hydrogen cyanide, thiophenol and 2-nitropropane. The reactions proceeded without difficulty and the physical properties of the adducts are listed in Table I.

Compounds IIIa-IIIg and IIIi were tested in the maximal electroshock seizure and subcutaneous pentylenetetrazol seizure threshold tests for anticonvulsant activity and in the rotorod test for neurotoxicity in male mice [3] by reported procedures [4]. Compound IIIh was not tested.

Table I

Physical Properties of 1-Aryl-3-methylene-2-pyrrolidinone Adducts III

Compound	X	R	Mp, °C	Yield, %	Formula	Analysis, % Calcd./Found C	H	N
IIIa	*p*-CH_3	CN	116-117 [a]	52	$C_{13}H_{14}N_2O$	72.87	6.59	13.07
						72.78	6.60	13.15
IIIb	p-CH_3	$C(CH_3)_2NO_2$	114-116 [b]	31	$C_{15}H_{20}N_2O_3$	65.20	7.30	10.14
						65.44	7.21	10.01
IIIc	*p*-Br	CN	113-114 [a]	70	$C_{12}H_{11}BrN_2O$	51.63	3.97	10.04
						51.90	4.18	9.81
IIId	*p*-Br	SC_6H_5	97.5-98 [c]	76	$C_{17}H_{16}BrNOS$	56.36	4.45	3.87
						56.07	4.61	3.69
IIIe	*p*-Br	$C(CH_3)_2NO_2$	95-97 [b]	74	$C_{14}H_{17}BrN_2O_3$	49.28	5.02	8.21
						49.05	5.05	8.03
IIIf	*o*-Cl	$C(CH_3)_2NO_2$	140-141.5 [d]	50	$C_{14}H_{17}ClN_2O_3$	56.67	5.77	9.44
						56.42	5.79	9.29
IIIg	*m*-Cl	SC_6H_5	60-61 [b]	89	$C_{17}H_{16}ClNOS$	64.24	5.07	4.41
						64.32	5.51	4.20
IIIh	*p*-F	CN	96.5-97 [a]	40	$C_{12}H_{11}FN_2O$	66.05	5.08	12.84
						65.85	5.15	12.82
IIIi	*p*-F	OCH_3	54.5-56.5 [e]	64	$C_{12}H_{14}FNO_2$	64.56	6.32	6.27
						64.80	6.17	6.32

[a] Cyclohexane-toluene. [b] 95% Ethanol. [c] Methanol. [d] Ethanol-water. [e] Petroleum ether (bp 30-60°).

None of the compounds showed activity at 100 mg/kg in either test. In the maximal electroshock seizure test, IIIe and IIIi exhibited activity at 600 mg/kg, however, IIIi also showed toxicity at this dose. In the pentylenetetrazole seizure test, IIIe displayed activity at 300 mg/kg with no toxicity. Compounds IIIb and IIIi were active in the same test at 600 mg/kg and there was no toxicity shown by IIIb at this dose. A greater percentage (3/8) of adducts III showed activity as compared to the starting 3-methylene compounds I (1/8).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The ir spectra were taken on a Perkin-Elmer 700 spectrophotometer as either liquid films or as potassium bromide pellets. The nmr spectra were recorded on a Varian EM-360 spectrometer, using tetramethylsilane as the internal reference. Mass spectra were obtained on a RMU-7 double-focusing spectrometer by Hitachi/Perkin-Elmer. Elemental analyses for carbon, hydrogen and nitrogen were performed by Microanalysis, Inc., Wilmington, Delaware. Compounds exhibited ^{1}H-nmr and mass spectra consistent with the structures shown.

Hydrogen Cyanide Adducts.

Compound IIIc was prepared by the dropwise addition of 6.25 ml of hydrochloric acid to an ice-cold suspension of 6.25 g of sodium cyanide in 25 ml of dimethylformamide, followed immediately by the addition of 1.26 g (0.005 mole) of 1-(*p*-bromophenyl)-3-methylene-2-pyrrolidinone [1]. The mixture was kept at room temperature for 24 hours and poured into water and filtered. The cholocate colored solid was air dried overnight, and recrystallized from toluene-cyclohexane (charcoal) affording 0.98 g (70%) of white crystals, mp 113-114°.

Thiophenol Adducts.

Compound IIId was prepared by storing a mixture of 1.51 g (0.006 mole) of 1-(*p*-bromophenyl)-3-methylene-2-pyrrolidinone [1], 2 ml of thiophenol and 8 ml of pyridine for 87 hours at room temperature. Pouring into water gave a white precipitate which was filtered and recrystallized from methanol yielding 1.66 g (76%) of silvery white plates, mp 97.5-98°.

2-Nitropropane Adducts.

Compounds IIIf was obtained by storing a mixture of 1.25 g (0.006 mole) of 1-(*o*-chlorophenyl)-3-methylene-2-pyrrolidinone [1], 2 ml of 2-nitropropane, 8 ml of tetrahydrofuran and 8 drops of benzyltrimethylammonium hydroxide (40% in methanol) for 7 days at room temperature. The mixture was poured into water acidified with hydrochloric acid. Scratching and cooling gave a solid which was recrystallized from aqueous ethanol producing 0.89 g (50%) of white solid, mp 140-141.5°.

Methanol Adducts.

Compounds IIIi was prepared by adding 1.15 g (0.006 mole) of 1-(*p*-fluorophenyl)-3-methylene-2-pyrrolidinone [1] to 8 ml of methanol in which a small piece (3 mm^3) of sodium had been dissolved. The resulting mixture was stored at room temperature for 5 days and then poured into water acidified with hydrochloric acid. Sodium bicarbonate and sodium chloride were added and the organic solid which appeared was filtered. Recrystallization from petroleum ether (bp 30-60°) gave 0.85 g (64%) of white crystals, mp 54.5-56.5°.

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REFERENCES AND NOTES

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