to offer any advantage over hydrochloric acid for chromatography.

The recommended procedure for purifying mussel poison concentrates by chromatographic fractionation on acid-washed Norit A is based on experience gained from carrying out over one hundred chromatograms. Though it is difficult to obtain exactly duplicate results even with aliquots of the same material on columns prepared in an identical manner, the average total recovery of poison in chromatography is from 60–80%. The most toxic fraction of the eluate contains 30–50% of the poison. This fraction will often show an enrichment of as great as twenty-fold if the starting material is a concentrate obtained by ion exchange on Decalso and as great as seventy-five-fold if the starting material is a crude, partially decolorized mussel poison extract. Poison concentrates obtained from ion exchange on Decalso contain 50–70% of the poison in the crude extract and usually have a toxicity of 0.07–0.14 MU./γ. Chromatography of these eluates on acid-washed Norit A results in a recovery of 30–50% of this poison with a toxicity greater than 1 MU./γ. The over-all recovery of poison with a toxicity greater than 1 MU./γ, after purification by ion exchange on Decalso and subsequent chromatography on acid-washed Norit A, is 18–30%.

Summary

1. A procedure is described for the chromatographic fractionation of mussel poison concentrates on active carbon.

2. Repeated use of carbon columns for the chromatographic fractionation of mussel poison hydrochloride usually results in a better recovery of poison as well as in fractions of higher toxicity.

3. The adsorption behavior of mussel poison on active carbon varies widely with different anions.

4. By chromatography on Norit A of mussel poison concentrates obtained from ion exchange on Decalso, it is possible to obtain a 30–50% yield of twenty-fold enriched material with a toxicity greater than 1 MU./γ.

5. The chromatography of partially decolorized, defatted, crude mussel poison extracts on Norit A yields 30–50% of seventy-five-fold enriched material.

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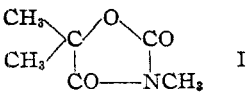
[CONTRIBUTION FROM ABBOTT LABORATORIES]

Some N-Alkyl-2,4-oxazolidinediones and their Anticonvulsant Properties

BY M. A. SPIELMAN AND GUY M. EVERETT

An earlier communication[1] has described the synthesis of some N-alkyl derivatives of 2,4-oxazolidinedione and their effect as analgesic agents. Subsequently, Everett and Richards[2] investigated the anticonvulsant properties of this type of compound, and as an outgrowth of their studies 3,5,5-trimethyl-2,4-oxazolidinedione under the trade name Tridione (I) has come into wide use in the treatment of petit mal epilepsy.[3] This paper presents results obtained in an expansion of the series.



I

The new N-alkyl-2,4-oxazolidinediones are much like those previously reported. They are liquids or low-melting solids, neutral in reaction and rapidly destroyed by strong aqueous alkali. They were synthesized along conventional lines as described below.

Experimental Part[4]

The parent 2,4-oxazolidinediones were prepared by the Stoughton method[5] in which an α-hydroxyester is condensed with urea by means of sodium ethoxide.

One α-hydroxyester is new. Methyl *n*-propyl ketone cyanhydrin on alcoholysis gave ethyl α-hydroxy-α-methylvalerate; b. p. 91–95° at 40 mm., $n^{25}D$ 1.4135. *Anal.* Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.09. Found: C, 59.84; H, 9.88.

The following three new 2,4-oxazolidinediones were prepared by condensing the appropriate α-hydroxyester with urea.[5]

5-*n*-Propyl-2,4-oxazolidinedione boiled at 122–127° at 0.5 mm. After three crystallizations from ether–petroleum ether it formed thin blades which melted at 53–55°. *Anal.* Calcd. for $C_6H_9NO_3$: N, 9.80. Found: N, 9.63.

5-Isopropyl-2,4-oxazolidinedione boiled at 118–119° at 1.5 mm., $n^{25}D$ 1.4671. *Anal.* Calcd. for $C_6H_9NO_3$: N, 9.80. Found: N, 9.87.

5-Methyl-5-*n*-propyl-2,4-oxazolidinedione is a thick, colorless oil; b. p. 115–118° at 1 mm., $n^{25}D$ 1.4583. *Anal.* Calcd. for $C_7H_{11}NO_3$: N, 8.91. Found: N, 8.75.

N-Methylation was carried out with dimethyl sulfate as described before[1] except that the use of methanol as solvent gave more consistent yields.

Introduction of higher alkyls by reaction of silver salts with alkyl iodides[1] gave poor yields and the method was soon abandoned.[6] Better results were obtained by preparing the potassium salt of the 2,4-oxazolidinedione in Cellosolve (glycol monoethyl ether) and heating with the appropriate halide. Chlorides, bromides and iodides were substantially equivalent, although with iodides it was found best to add the halide slowly to the cooled solution or suspension of the salt.

(1) Spielman, THIS JOURNAL, **66**, 1244 (1944).

(2) Everett and Richards, *J. Pharmacol.*, **81**, 402 (1944).

(3) Lennox, *J. Am. Med. Assoc.*, **129**, 1069 (1945); Perlstein and Andelman, *J. Pediatrics*, **29**, 20 (1946).

(4) Microanalyses by E. F. Shelberg. Compound 7 was made by W. B. Brownell. We are indebted to A. H. Smith, Jr., for technical assistance.

(5) Stoughton, THIS JOURNAL, **63**, 2376 (1941).

(6) Hook, *Nature*, **160**, 610 (1947), in a note which has just come to our attention has shown that the silver salt method may lead to O-alkylation.

TABLE I

DERIVATIVES OF 2,4-OXAZOLIDINEDIONE

No.	3-Substituent	3,5-Substituents	M. p., °C.	B. p. °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found
1	C_2H_5	H, H		133–136[a]	32	1.4619	$C_5H_7NO_3$		
2	n-C_3H_7	H, H		142–147	32	1.4602	$C_6H_9NO_3$	9.78	9.60
3	s-C_5H_{11}	H, H		97–100	1.5	1.4585	$C_8H_{13}NO_3$	8.19	7.81
4	i-C_5H_{11}	H, H		157–162	35	1.4587	$C_8H_{13}NO_3$	8.19	8.16
5	C_2H_5	H, CH_3		140–145	60	1.4519	$C_6H_9NO_3$	9.78	9.67
6	CH_2=$CHCH_2$	H, CH_3		137–140	35	1.4688	$C_7H_9NO_3$	9.02	8.95
7	CH_3	H, C_2H_5		160–165	100	1.4567	$C_6H_9NO_3$	9.78	9.63
8	$C_6H_5CH_2$	H, CH_3	74–76				$C_{11}H_{11}NO_3$	6.83	6.65
9	CH_3	H, n-C_3H_7		99–101	3	1.4567	$C_7H_{11}NO_3$	8.92	8.89
10	CH_3	H, i-C_3H_7		118–119	18	1.4554	$C_7H_{11}NO_3$	8.92	8.92
11	CH_3	CH_3, n-C_3H_7		135–138	35	1.4498	$C_8H_{13}NO_3$	8.19	8.30
12	n-C_3H_7	CH_3, CH_3	47–48	120–124	28		$C_8H_{13}NO_3$	8.19	8.13
13	s-C_5H_{11}	CH_3, CH_3		142–147	50	1.4410	$C_{10}H_{17}NO_3$	7.05	7.02
14	$HOOCCH_2$	CH_3, CH_3	114–116				$C_7H_7NO_5$	7.49	7.47
15	$(C_2H_5)_2N(CH_2)_2$	CH_3, CH_3		108–110	1	1.4545	$C_{11}H_{20}N_2O_3$	12.28	12.07[b]

[a] Ahlquist, *J. prakt. Chem.*, 99, 45 (1919), gives 119.5° at 12 mm. [b] The hydrochloride melted at 192°. *Anal.* Calcd. for $C_{11}H_{21}ClN_2O_3$: N, 10.60. Found: N, 10.75.

Typically, to 100–150 cc. of Cellosolve in a 3-neck flask assembly was added 0.2 mole of the 2,4-oxazolidinedione and 13 g. of potassium hydroxide pellets with heating to effect solution. To the refluxing mixture 0.2 mole of the halide was added dropwise. Heating was continued one hour. The solution was cooled, filtered, and the solvent was removed under diminished pressure. The product was taken up in ether, washed with sodium bicarbonate solution, dried and distilled. Yields were 50% or better with primary halides and less with secondary halides. No individual reaction was studied extensively with the idea of obtaining maximum yield.

The 5,5-dimethyl-2,4-oxazolidinedione-3-acetic acid was prepared in 40% yield by refluxing the sodium salt of the 5,5-dimethyl-2,4-oxazolidinedione and sodium chloroacetate in water for sixteen hours with subsequent acidification. It was crystallized from benzene.

Physical properties and analyses are shown in Table I.

Pharmacology

The compounds were tested for their ability to suppress in mice the convulsions induced by Metrazole (pentamethylenetetrazole) or electroshock. The method was that described in the earlier work[2] and was considered adequate as a preliminary test for the two types of anticonvulsant activity. The compounds of the present series are low in toxicity and mildly depressing. They were administered in doses up to those producing ataxia, and it may be seen in Table II that only a few compounds have anticonvulsant activity and only at levels where ataxia was evident. The results are in contrast to those obtained from 3,5,5-trimethyl-2,4-oxazolidinedione (Tridione), 3,5-dimethyl-2,4-oxazolidinedione and 5-ethyl-3,-5-dimethyl-2,4-oxazolidinedione which are particularly active against Metrazole, and which have been demonstrated in clinical trial to have antiepileptic action against petit mal.

An interesting observation in the series is that compound 13, 5,5-dimethyl-3-s-amyl-2,4-oxazolidinedione, is not depressing as are the other compounds but instead exerts a stimulating effect and at high levels produces convulsions. On the other hand, compound 15, which has the diethylaminoethyl group on the nitrogen atom and therefore might reasonably be expected to prove stimulating, is practically devoid of pharmacological activity.

TABLE II

ANTICONVULSANT ACTIVITY IN MICE

No.	Dose, mg./kg.	Symptoms	Protection Metrazole	Protection Electroshock
1	1500	None	−	
2	400	Ataxia	+	+
3	200	Ataxia	−	−
4	200–800	Slight ataxia	−	+
5	400	Ataxia	−	−
6	100	Ataxia	−	−
7	400	Ataxia	+	−
8	400	Ataxia	−	−
9	200	Ataxia	−	−
10	200	Ataxia	−	−
11	400	Ataxia	−	−
12	200	Ataxia	−	−
13	800	Excitement	−	−
14	800	None	−	−
15	1000	None	−	−

Summary

A series of N-substituted derivatives of 2,4-oxazolidinedione has been prepared and tested for anticonvulsant activity. None has sufficient potency to be of therapeutic interest.

NORTH CHICAGO, ILLINOIS RECEIVED NOVEMBER 6, 1947