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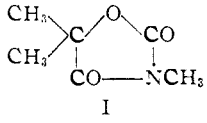
Some Analgesic Agents Derived from Oxazolidine-2,4-dione

BY M. A. SPIELMAN

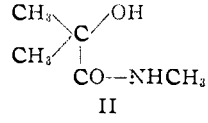
There is little known about the correlation between the structure of organic substances and their analgesic action. Consequently, during the several years of our search for new analgesic agents, many different compounds were tested, and among them was a series of substituted oxazolidine-2,4-diones. The present paper describes their synthesis and reports briefly on their pharmacological properties.

The derivatives of oxazolidine-2,4-dione have long been known,[1] but not until recently have they been investigated for possible therapeutic use. Erlenmeyer[2] predicted and demonstrated hypnotic effects in a small series of compounds, and Stoughton,[1a] with others, has shown that 5,5-di-*n*-propyloxazolidine-2,4-dione (Propazone), in particular, is a potent, long-acting hypnotic and anti-convulsant agent.[3]

In this Laboratory we have confirmed the pronounced hypnotic action of several 5,5-dialkyloxazolidine-2,4-diones, but all were found to be practically devoid of analgesic properties, even when negligible sedation was produced. Alkylation of the nitrogen atom, however, produced a marked qualitative change in physiological response. A strong analgesic effect appeared, and in the compounds of relatively low molecular weight it was not masked by hypnosis. The outstanding compound is 3,5,5-trimethyloxazolidine-2,4-dione (I) which possesses an analgesic potency



I



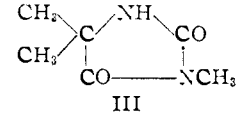
II

in the aspirin or amidopyrine range and has a remarkably low toxicity. It is effective orally or parenterally as demonstrated by the conventional test methods which are used with animals[4] and man.[5] Richards and Everett[6] have published a preliminary note on the drug, and details will appear later. Studies of anti-convulsant effects are in progress.

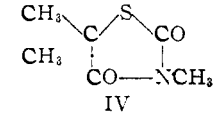
The oxazolidine-2,4-diones used for N-alkylation were all prepared by literature methods. The only new compound is 5,5-pentamethylene-oxazolidine-2,4-dione which was made by the procedure of Traube and Ascher[7] from guanidine and ethyl 1-hydroxycyclohexanecarboxylate. Methylations were carried out with dimethyl sulfate and alkali. Methyl *p*-toluenesulfonate was tried and found to give very poor yields. The N-ethyl radical was introduced by the action of ethyl iodide on the silver salt of the parent compound. All N-alkyl derivatives are new. Physical properties and analytical data are in Table I.

The N-alkyloxazolidine-2,4-diones are neutral, low-melting compounds which are fairly stable to aqueous acids, even on boiling, but are rapidly hydrolyzed by alkali at room temperature.[8] In fact, trimethyloxazolidine-2,4-dione reacts with such speed that a convenient assay method is based upon titration with sodium hydroxide. With phenolphthalein as indicator it behaves as a monobasic acid, and the product is N-methyl-α-hydroxyisobutyramide (II).

For comparison of physiological properties, 3,5,5,-trimethylhydantoin (III) and 3,5,5-trimethylthiazolidine-2,4-dione (IV) were made by similar methods. They are, respectively, the nitrogen and sulfur analogs of I, and were found to be without important pharmacological attributes except that IV is weakly hypnotic.



III



IV

Experimental Part

3,5,5-Trimethyloxazolidine-2,4-dione.—The preparation of this compound is typical of the methylation procedure. In a 3-neck flask was placed 72 g. of 5,5-dimethyloxazolidine-2,4-dione, 30 g. of sodium hydroxide and 400 cc. of water. With vigorous stirring and external cooling 85 g. (10% excess) of dimethyl sulfate was added dropwise. The temperature was kept below 40°. After one hour of stirring the mixture was extracted with ether and the ether extract distilled; b. p. 78–80° at 5 mm. It soon solidified and was recrystallized from 50% methanol or by freezing out of ethyl ether. Yields were consistently 30–40% in spite of many modifications in the procedure such as the use of larger or smaller amounts of alkali, the substitution of sodium carbonate for sodium hydroxide, a reverse order of addition, etc. Methylation of the higher members of the series, however, gave yields in the range of 50–65%.

3,5,5-Trimethyloxazolidine-2,4-dione is the compound of principal interest in this work and hence was most studied. When pure, it possesses a burning, faintly bitter taste and has a mild camphoraceous odor. It is about 5% solu-

(1) (a) For leading references to preparative methods see Stoughton, THIS JOURNAL, **63**, 2376 (1941); also (b) Lambling, *Bull. soc. chim.*, [3] **27**, 441, 606 (1902); (c) Ahlqvist, *J. prakt. Chem.*, **99**, 45 (1919); (d) Aspelund, *C. A.*, **35**, 2143 (1941); **37**, 6250 (1943); (e) German Patent 728,036; *C. A.*, **37**, 6675 (1943); German Patent 729,851; *Chem. Zentr.*, I, 2007 (1943); (f) U. S. Patents 2,338,064, 2,338,220, 2,349,313, 2,349,795, 2,349,796.

(2) Erlenmeyer, *Helv. chim. Acta*, **21**, 1013 (1938).

(3) Luton, Blalock, Baxter and Stoughton, *Proc. Soc. Exptl. Biol. Med.*, **47**, 245 (1941); Tainter, *et al.*, *J. Pharmacol.*, **79**, 42 (1943).

(4) Macht and Macht, *J. Am. Pharm. Assoc.*, **29**, 193 (1940); D'Amour and Smith, *J. Pharmacol.*, **72**, 74 (1941); Andrews and Workman, *ibid.*, **73**, 99 (1941); Kueter and Richards, *J. Lab. Clin. Med.*, **28**, 1585 (1943).

(5) Hardy, Wolff and Goodell, *J. Clin. Investigation*, **19**, 649 (1940).

(6) Richards and Everett, Federation Proceedings, Federation of American Societies for Experimental Biology, Vol. 3, No. 1, p. 39 (1944).

(7) Traube and Ascher, *Ber.*, **46**, 2077 (1913).

(8) In this connection compare 1c, p. 78.

TABLE I

DERIVATIVES OF OXAZOLIDINE-2,4-DIONE

3-Substituent	5,5-Substituents	M. p., °C.	B. p., °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found
CH_3	H, H	128	.....	..	....	$C_4H_5NO_3$	12.2	12.2
CH_3	H, CH_3	...	140–144	50	1.4574	$C_5H_7NO_3$	10.8	10.9
CH_3	$(CH_3)_2$	46	78–80	5	....	$C_6H_9NO_3$	9.7	10.0
C_2H_5	$(CH_3)_2$	61	.....	..	....	$C_7H_{11}NO_3$	8.9	8.8
CH_3	CH_3, C_2H_5	...	101–102	11	1.4507	$C_7H_{11}NO_3$	8.9	8.8
CH_3	$(C_2H_5)_2$	...	105–108	11	1.4500	$C_8H_{13}NO_3$	8.2	8.1
CH_3	$(n\text{-}C_3H_7)_2$	46	100–105	4	....	$C_{10}H_{17}NO_3$	7.0	7.1
CH_3	$-(CH_2)_5-$	95	.....	..	....	$C_9H_{13}NO_3$	7.7	7.8

ble in water at room temperature and is very soluble in the usual organic solvents except petroleum ether. The water solubility is markedly increased by the addition of urethan.

Hydrolysis is the basis of an assay method. To 20 ml. of 0.05 *N* solution was added 28.5 ml. of 0.1 *N* sodium hydroxide; immediate back titration (phenolphthalein) required 18.5 ml. 0.1 *N* hydrochloric acid; theory, 18.5 ml. That hydrolysis leads to N-methyl-α-hydroxyisobutyramide was established by exhaustive ether extraction of the hydrolysis mixture. The product is very soluble in water and sparingly soluble in ether from which it was recrystallized; m. p. 78–79° *Anal.* Calcd. for $C_5H_{11}NO_2$: N, 12.0. Found: N, 12.0.

3-Ethyl-5,5-dimethyloxazolidine-2,4-dione.—Twenty grams of 5,5-dimethyloxazolidine-2,4-dione was dissolved in 50 cc. of water, neutralized with 6.7 g. of sodium hydroxide and treated with 26 g. of silver nitrate in a minimum of water. The precipitated silver salt was washed and vacuum dried at 50°; yield, 32 g. It was suspended in 200 cc. of dry ether, and 20 g. of ethyl iodide was added. The mixture was left for three days in a stoppered flask which was shaken occasionally. The product which was isolated in nearly quantitative yield boiled at 95–102° at 3 mm. It was crystallized from dilute alcohol; m. p. 61–62°. The same reaction failed with alcohol as solvent as did several attempts at ethylation with diethyl sulfate.

5,5-Pentamethyleneoxazolidine-2,4-dione.—The Traube and Ascher[7] procedure was used with little modification. Ethyl 1-hydroxycyclohexanecarboxylate[9] and guanidine condensed spontaneously in concentrated alcoholic solution. A 0.1 mole run was diluted with several volumes of ether and extracted with 150 cc. of 15% hydrochloric acid. The aqueous phase was boiled under a reflux for one hour and on cooling the product separated in 80% yield; m. p. 110–112°. *Anal.* Calcd. for $C_8H_{11}NO_3$: N, 8.3. Found: N, 8.1.

3,5,5-Trimethylhydantoin.—To 50 g. of dimethylhydantoin and 22 g. of sodium hydroxide in 300 cc. of water was added with vigorous stirring 63 g. of dimethyl sulfate. On cooling in ice-salt, 17 g. of needles separated and 10 g. more was isolated by extraction with ether; m. p. 149°. Bailey and Randolph[10] give the same melting point for a product obtained in two steps from α-aminoisobutyric acid and methyl isothiocyanate. *Anal.* Calcd. for $C_6H_{10}N_2O_2$: N, 19.7. Found: N, 19.9.

3,5,5-Trimethylthiazolidine-2,4-dione.—Sixteen grams of 5,5-dimethylthiazolidine-2,4-dione[11] was methylated with 15.6 g. of dimethyl sulfate and 6.5 g. of sodium hydroxide in 100 cc. of water. The yield was 40%; m. p. 49–51°. *Anal.* Calcd. for $C_6H_9NO_2S$: N, 8.8. Found: N, 8.6.

Summary

A series of tri-substituted derivatives of oxazolidine-2,4-dione has been synthesized for pharmacological study. 3,5,5-Trimethyloxazolidine-2,4-dione is an effective analgesic.

3,5,5-Trimethylhydantoin and 3,5,5-trimethylthiazolidine-2,4-dione are without analgesic properties.

(9) Auwers and Krollpfeiffer, *Ber.*, **48**, 1389 (1915).

(10) Bailey and Randolph, *ibid.*, **41**, 2504 (1908).

(11) Wheeler and Barnes, *Am. Chem. J.*, **24**, 79 (1900).

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The Nitration of 4-Phenylphenyl Acetate

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The behaviors of 4-phenylphenyl benzoate[1] and 4-phenylphenyl 4-toluenesulfonate[2] when nitrated are analogous to the reactions encountered when that benzoate[3] and 4-phenylphenyl benzenesulfonate[4] are brominated. In each instance the entering substituent goes to that position in the ester molecule most remote from the acyloxy group. The bromination of 4-phenylphenyl acetate,[5] on the other hand, parallels the bromination of 4-phenylphenol.[6] Further, the nitration of 4-phenylphenol yields 2-nitro-4-phenylphenol.

By procedures as similar as possible to those employed in earlier studies, the nitration of 4-phenylphenyl acetate has been investigated; several sets of conditions were employed. The acetate is more difficult to nitrate than 4-phenylphenol, for, attempting to nitrate the ester under those conditions required for the formation of 2-nitro-4-phenylphenol from 4-phenylphenol, no substitution was effected, and starting material

(1) Hazlet and Van Orden, THIS JOURNAL, **64**, 2505 (1942).

(2) Bell and Kenyon, *J. Chem. Soc.*, 3049 (1926).

(3) Hazlet, Alliger and Tiede, THIS JOURNAL, **61**, 1447 (1939).

(4) Hazlet, *ibid.*, **59**, 1087 (1937).

(5) Hazlet and Kornberg, *ibid.*, **61**, 3037 (1939).

(6) (a) Raiford and Colbert, *ibid.*, **47**, 1457 (1925); (b) Colbert and others, *ibid.*, **56**, 202, 2128 (1934).