reaction is in agreement with previous observations on ethyleneimines.[5]

The molecular refractivity as calculated with the Lorentz–Lorenz equation is 22.41. The value obtained from the structural formula is 22.412.

Anal. Calcd. for C_4H_9N: C, 67.5; H, 12.8. Found: C, 67.3; H, 13.0.

This amine was also obtained in 7% yield by the treatment of the hydrochloride of 2-chloroethylethylamine with 40% aqueous sodium hydroxide.

Picrate.—Fine yellow needles, melting when dry at 111°.

Chloroaurate.—The amine forms with chloroauric acid a light yellow precipitate which decomposes sharply at 104°.

Hydrochloride.—The evaporation of N-ethylethyleneimine with an excess of hydrochloric acid results in the formation of the hydrochloride of 2-chlorethylethylamine. Three crystallizations from *n*-butanol yielded a pure white product which melted at 223°. An intimate mixture of this with the known hydrochloride of 2-chlorethylethylamine melted at 223°.

(5) British Patent 501,595; *Chem. Abs.*, **33**, 6479 (1939).

Anal. Calcd. for $C_4H_{11}NCl_2$: ionizable chlorine, 24.62; total chlorine, 49.24. Found: ionizable chlorine, 24.73; total chlorine content, 49.69.

Summary

1. N-Ethylethyleneimine has been obtained from the reaction of 2,2′-dichlorodiethylamine with metallic sodium. Its properties have been studied briefly and a few derivatives prepared. The presence of N-vinylethyleneimine also was indicated.

2. The hydrochloride of 2-chlorethylethylamine obtained by the evaporation of N-ethylethyleneimine with hydrochloric acid has been compared with the same compound prepared by another method.

3. N-Ethylethyleneimine and 2-chloroethylethylamine hydrochloride are apparently new to literature.

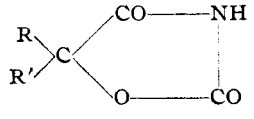
MOSCOW, IDAHO RECEIVED MAY 3, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE]

5,5-Dialkyl-2,4-oxazolidinediones[1,2]

BY ROGER W. STOUGHTON

In a recent study of diacylureas,[3] we made the observation that the properties of the diureides derived from simple aliphatic acids differed from those of a group of compounds reported by Clemmensen and Heitman[4] as diureides of α-hydroxy acids. The latter had been prepared by the condensation of the ethyl ester of an α-hydroxy acid with urea in the presence of sodium ethylate, a procedure by which it is impossible to prepare simple diureides. Consequently, this condensation was repeated, and while the products which were obtained were similar in general properties to those described by Clemmensen and Heitman, the analytical data indicated that they were not diureides but might be substituted oxazolidinediones. A comparison of the product obtained from the condensation of ethyl lactate and urea with a sample of 5-methyl-2,4-oxazolidinedione prepared by the method of Traube and Ascher[5] showed these two substances were identical. After this part of the work had been completed, the same conclusion was reported independently by Aspelund[6] while working with the hydrolysis products of certain dialuric acids. Therefore, the hydroxy diureides of Clemmensen and Heitman are actually 5-substituted-2,4-oxazolidinediones.



Only a few of these 2,4-oxazolidinediones are recorded in the literature. They have been prepared by the action of bromine water or lead acetate on 2-thio-4-oxazolidone[7]; by the condensation of an α-hydroxy ester with guanidine and the subsequent hydrolysis of the 2-imino-4-oxazolidone[5,8]; by the reaction of ethyl chlorocarbonate and the amide of an α-hydroxy acid[9]; and by the action of alkali on an α-substituted-α-bromoacetylurea.[10]

(1) Presented before the Division of Medicinal Chemistry at the St. Louis meeting of the American Chemical Society, April 10, 1941.

(2) This investigation was supported by a grant from the Mallinckrodt Chemical Works, St. Louis, Missouri.

(3) Stoughton, *J. Org. Chem.*, **2**, 514 (1938).

(4) Clemmensen and Heitman, *Am. Chem. J.*, **40**, 280 (1908); **42**, 319 (1909).

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

(6) Aspelund, *Acta Acad. Aboensis, Math. et Phys.*, **11**, no. 7 (1938); **11**, no. 14 (1939).

(7) (a) Urech, *Ber.*, **11**, 467 (1878); **13**, 485 (1880); (b) Ahlquist, *J. prakt. Chem.*, **99**, 45 (1919); (c) Erlenmeyer, Kleiber and Loebenstein, *Helv. Chim. Acta*, **21**, 1010 (1938).

(8) Erlenmeyer and Kleiber, *ibid.*, **21**, 111 (1938).

(9) Altwegg and Ebin, U. S. Patent 1,375,949 (1921); British Patent 159,153 (1920).

(10) Newberry, *J. Chem. Soc.*, **127**, 295 (1925).

Because of the close structural relationship between the 5,5-dialkyl-2,4-oxazolidinediones and other compounds possessing hypnotic action, it was decided to prepare some of the higher alkyl derivatives and study their pharmacological properties. Of the synthetic methods available, the condensation of an α-hydroxy ester with urea in the presence of sodium ethylate was found to give the most satisfactory results. Presumably, the monoureide is first formed and then ammonia splits off to give the oxazolidinedione. The α-hydroxy esters were prepared from the corresponding ketone by the addition of hydrogen cyanide, followed by hydrolysis first to the amide and then to the acid and by final esterification. Two amides, those derived from diisopropyl and *t*-butyl methyl ketones, were so resistant to hydrolysis that it was found more convenient to prepare the oxazolidinedione directly from the amide by reaction with ethyl chlorocarbonate according to the method of Altwegg and Ebin.[9]

Three different types have thus far been made. In the first of these, one R is always a methyl group while R′ is some other alkyl group; in the second type, both R and R′ are identical alkyl groups; and in the third, one R is always a phenyl group while R′ is an alkyl group. These substances are mostly low-melting solids although a few are oils at room temperature. However, they could be purified by distillation under reduced pressure without decomposition. They are very slightly soluble in cold water but very soluble in oils and organic solvents, even in warm petroleum ether. The hydrogen on the nitrogen is acidic and can be titrated readily with phenolphthalein to a sharp end-point. Stable metallic salts are formed when the oxazolidinediones are treated with alkali hydroxides or carbonates. Aqueous solutions of the sodium salts are stable except under prolonged boiling.

Our pharmacological studies show that on intravenous administration of the sodium salts of the dialkyl oxazolidinediones to white mice a marked anesthetic action, usually of brief duration, was produced. The most active compounds were those that contained a total of eight to ten carbon atoms in the substituents of the 5-position and were comparable in activity to the dialkyl barbituric acids. A few compounds containing highly branched chains were convulsants. One compound, the 5,5-di-*n*-propyl-2,4-oxazolidinedione, was found to have an intense hypnotic action of long duration although this compound was not as active as others in producing deep anesthesia. The median anesthetic and lethal doses of these substances are listed in Table II of the Experimental Part. More complete pharmacological studies are being published elsewhere.

Experimental Part

Preparation of Ketones.—Those ketones which were not available were prepared by well-known synthetic methods, the methyl alkyl ketones by the acetoacetic ester synthesis and the phenyl alkyl ketones by the Friedel–Crafts synthesis.

5-Methyloctanone-2 has not been reported previously and was prepared according to the procedure described in "Organic Syntheses"[11] from 1-bromo-2-methylpentane and ethyl acetoacetate. It boiled at 100–102° at 50 mm. pressure. The semicarbazone crystallized from dilute methanol in colorless plates and melted at 128–129° (cor.).

Anal. Calcd. for $C_{10}H_{21}N_3O$: N, 21.09. Found: N, 20.88.

Dialkylglycolic Acids.—The preparation of the aliphatic dialkylglycolic acids from the corresponding ketones is illustrated by the following procedure. The entire reaction was carried out in a good hood. In a round-bottom flask, cooled in an ice-bath and protected by a spiral condenser cooled in ice water, was placed 1.2 moles (33 g.) of liquid hydrogen cyanide, prepared according to "Organic Syntheses"[11] (p. 307) and condensed directly into the flask. One mole of the proper ketone, to which had been added 0.5 cc. of piperidine, was then added to the hydrogen cyanide over a period of ten minutes. The mixture was shaken occasionally and allowed to stand for one hour at 0°. After the condenser had been replaced by a mechanical stirrer and the flask cooled in an ice–salt-bath, 190 cc. of concentrated sulfuric acid, which had been diluted with 19 cc. of water and previously cooled, was added over a period of ten minutes with vigorous stirring. The bath was maintained at 0° for three to five hours and then allowed to stand at room temperature overnight. The next morning the mixture was poured into cracked ice and the amide separated. This was collected and steam distilled to remove any unreacted ketone. As most of these amides are new, analytical samples were saved and purified by recrystallization from benzene or benzene and petroleum ether. The crude amide was hydrolyzed by refluxing with 20% sodium hydroxide solution or, if that failed to bring about hydrolysis, with 20% hydrochloric acid. The *t*-butyl methyl- and the diisopropyl-glycolamide were hydrolyzed very slowly even by hydrochloric acid and were not converted into the acid. The dialkylglycolic acids were finally purified either by distillation or by recrystallization from an appropriate solvent, usually petroleum ether. A yield of 60–80% usually was obtained. The physical characteristics of these acids and amides are given in Table I.

Phenyl Alkyl Glycolic Acids.—The cyanohydrins were prepared as before except that one mole of hydrogen cyanide and one-half mole of the proper phenyl alkyl ketone

(11) Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 343.

were used. After the addition was completed, 50 cc. of anhydrous ether was added and the mixture poured into 300 cc. of concentrated hydrochloric acid which was stirred vigorously and cooled in an ice–salt-bath. Dry, gaseous hydrogen chloride was passed into the mixture until it was thoroughly saturated. The bath was maintained at 0° for five hours and then the stirring was stopped and the reaction mixture allowed to stand overnight at room tem-

TABLE I

GLYCOLIC ACID DERIVATIVES

Glycolic acid derivative	Acid: M. p., °C. (cor.)	Acid: Formula	Acid: Neut. equiv. Calcd.	Acid: Neut. equiv. Found	Amide: M. p., °C. (cor.)	Amide: Formula	Amide: Nitrogen, % Calcd.	Amide: Nitrogen, % Found	Ethyl ester Boiling point °C.	Ethyl ester Boiling point Mm.
n-Butyl methyl	32–33	$C_7H_{14}O_3$	146.2	146.9	57– 58	$C_7H_{15}NO_2$	9.65	9.47	100–101	24
t-Butyl methyl	...	...	...	...	145–146[a]	$C_7H_{15}NO_2$	9.65	9.45	...	..
n-Amyl methyl	44– 45	$C_8H_{16}O_3$	160.2	160.0	64– 65	$C_8H_{17}NO_2$	8.80	8.70	112–113	23
Neopentyl methyl	108–109[b]	$C_8H_{16}O_3$	160.2	159.5	115–116	$C_8H_{17}NO_2$	8.80	8.62	92– 93	20
n-Hexyl methyl	39– 40[c]	$C_9H_{18}O_3$	174.2	174.3	58– 59	$C_9H_{19}NO_2$	8.09	7.90	101–102	5
n-Heptyl methyl	40– 41[c]	$C_{10}H_{20}O_3$	188.3	188.5	78– 79	$C_{10}H_{21}NO_2$	7.48	7.41	103–104	5
3-Methylhexyl methyl	47– 48	$C_{10}H_{20}O_3$	188.3	186.1	38– 39	$C_{10}H_{21}NO_2$	7.48	7.41	112–114	9
n-Octyl methyl	42– 43[c]	$C_{11}H_{22}O_3$	202.3	202.6	78– 79	$C_{11}H_{23}NO_2$	6.96	6.84	121–122	5
n-Nonyl methyl	46– 47[c]	$C_{12}H_{24}O_3$	216.4	216.2	86– 87	$C_{12}H_{25}NO_2$	6.50	6.56	125–127	3
Di-*n*-propyl	81– 82[d]	$C_8H_{16}O_3$	160.2	159.9	69– 70	$C_8H_{17}NO_2$	8.80	8.84	113–115	30
Diisopropyl	...	...	...	...	116–117	$C_8H_{17}NO_2$	8.80	8.70	...	..
Di-*n*-butyl	87– 88[e]	$C_{10}H_{20}O_3$	188.3	188.0	...	...	..	..	114–116	10
Diisobutyl	128–129[f]	$C_{10}H_{20}O_3$	188.3	187.5	138–139	$C_{10}H_{21}NO_2$	7.48	7.36	105–106	5
Di-*n*-amyl	76– 77	$C_{12}H_{24}O_3$	216.4	216.9	92– 93	$C_{12}H_{25}NO_2$	6.50	6.59	128–129	5
n-Propyl phenyl	93– 94	$C_{11}H_{14}O_3$	194.2	194.3	131–132	$C_{11}H_{15}NO_2$	7.25	7.50	124–125	3
n-Butyl phenyl	102–103	$C_{12}H_{16}O_3$	208.2	210.2	81– 82	$C_{12}H_{17}NO_2$	6.76	6.57	130–132	4
Isobutyl phenyl	112–113	$C_{12}H_{16}O_3$	208.2	209.6	129–130	$C_{12}H_{17}NO_2$	6.76	6.82	126–128	4
n-Amyl phenyl	102–103	$C_{13}H_{18}O_3$	222.3	224.0	93– 94	$C_{13}H_{19}NO_2$	6.33	6.28	143–145	4

[a] Richard, *Ann. chim. phys.*, **21**, 323 (1910). [b] Butlerow, *J. Russ. Phys.-Chem. Soc.*, **14**, 201 (1882). [c] Maehlmann, *Arb. Pharm. Inst. Univ. Berlin*, **11**, 107 (1914). [d] Prepared previously by several methods. [e] This compound was prepared from ethyl oxalate and *n*-butylmagnesium bromide using the general procedure of Hepworth, *J. Chem. Soc.*, **115**, 1206 (1919). [f] Basse and Klinger, *Ber.*, **31**, 1224 (1898); Bently and Perkin, *J. Chem. Soc.*, **73**, 66 (1898).

TABLE II

5,5-DIALKYL-2,4-OXAZOLIDINEDIONES AND THEIR ANESTHETIC ACTIVITY

2,4-Oxazolidinedione	Boiling point °C.	Boiling point Mm.	M. p., °C. (cor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	AD. 50,[d] mg./kg.	LD. 50, mg./kg.
5-*n*-Butyl-5-methyl-	148–151	4	...	$C_8H_{13}NO_3$	8.18	8.15	440	680
5-*t*-Butyl-5-methyl-	...		85– 86	$C_8H_{13}NO_3$	8.18	8.18	...[e]	750
5-*n*-Amyl-5-methyl-	149–150	3	25	$C_9H_{15}NO_3$	7.56	7.66	180	365
5-Neopentyl-5-methyl-	...		55– 56	$C_9H_{15}NO_3$	7.56	7.67	...[e]	900
5-*n*-Hexyl-5-methyl-	149–150	2	46– 47	$C_{10}H_{17}NO_3$	7.03	6.93	125	225
5-*n*-Heptyl-5-methyl-	155–156	2	32– 33	$C_{11}H_{19}NO_3$	6.57	6.51	95	145
5-Methyl-5-(3-methylhexyl)-	168–169	3	...	$C_{11}H_{19}NO_3$	6.57	6.36	85	155
5-Methyl-5-*n*-octyl-	...		62– 63	$C_{12}H_{21}NO_3$	6.16	6.26	70	125
5-Methyl-5-*n*-nonyl-	...		52– 53	$C_{13}H_{23}NO_3$	5.81	5.69	75	85
5,5-Dimethyl-[a]	...		76– 77	$C_5H_7NO_3$	10.85	10.87	400	450
5,5-Diethyl-[b]	146–147	6	28	$C_7H_{11}NO_3$	8.91	8.90	300	400
5,5-Di-*n*-propyl-	141–143	3	42– 43	$C_9H_{15}NO_3$	7.56	7.46	172	315
5,5-Diisopropyl-	...		86– 87	$C_9H_{15}NO_3$	7.56	7.53	...[e]	850
5,5-Di-*n*-butyl-	...		68– 69	$C_{11}H_{19}NO_3$	6.57	6.54	50	75
5,5-Diisobutyl-	150–151	3	...	$C_{11}H_{19}NO_3$	6.57	6.40	95	120
5,5-Di-*n*-amyl-	...		63– 64	$C_{13}H_{23}NO_3$	5.81	5.90	40	70
5-Methyl-5-phenyl-[c]	169–171	3	73– 74	$C_{10}H_9NO_3$	7.32	7.44	550	575
5-Ethyl-5-phenyl-[c]	174–176	3	61– 62	$C_{11}H_{11}NO_3$	6.83	6.97	200	300
5-Phenyl-5-*n*-propyl-	176–178	2	...	$C_{12}H_{13}NO_3$	6.39	6.64	140	205
5-*n*-Butyl-5-phenyl-	181–182	2	63– 64	$C_{13}H_{15}NO_3$	6.01	6.13	90	115
5-Isobutyl-5-phenyl-	184–186	3	...	$C_{13}H_{15}NO_3$	6.01	5.88	115	145
5-*n*-Amyl-5-phenyl-	199–200	3	...	$C_{14}H_{17}NO_3$	5.66	5.68	65	90
5,5-Diphenyl-	...		135–136	$C_{15}H_{11}NO_3$	5.53	5.71	135	135

[a] First prepared by Urech, ref. 7a. [b] See ref. 8. [c] Altwegg and Ebin report the m. p. of the methyl and ethyl phenyl derivatives as 70 and 63°, respectively; see ref. 9. [d] For details of the method of testing for anesthetic action see ref. 1. [e] Convulsant.

perature. By the next morning the crude amide had separated from the solution. This was collected, steam distilled to remove any unreacted ketone, and hydrolyzed as before. The yields varied from 40–60% of the theoretical based on the amount of ketone used. The individual compounds prepared are described in Table I.

Esterification of Glycolic Acids.—The substituted glycolic acids were esterified in the usual manner by refluxing with absolute ethyl alcohol saturated with dry hydrogen chloride. The approximate boiling points of these esters are given in Table I.

5-Methyl-2,4-oxazolidinedione.—To a cool solution of 11.5 g. (0.5 mole) of metallic sodium in 250 cc. of absolute alcohol was added 30 g. (0.5 mole) of dry urea and 56 g. (0.5 mole) of ethyl lactate. This mixture was refluxed on the steam-bath for fifteen hours, and as much alcohol as possible was removed under diminished pressure. The gummy residue was cooled and dissolved in 500 cc. of ice water. This aqueous solution was extracted with two 50-cc. portions of ether and acidified with hydrochloric acid. The product was taken up in ether and purified by distillation under reduced pressure. The fraction boiling at 147–148° at 5 mm. was collected and on standing crystallized to a colorless solid melting at 48–50° (cor.). The yield amounted to 44 g. (81%). This compound gave no lowering of the melting point of a sample of 5-methyl-2,4-oxazolidinedione prepared by the method of Traube and Ascher.[5]

Anal. Calcd. for $C_4H_5NO_3$: N, 12.17; neut. equiv., 115.1. Found: N, 12.05; neut. equiv., 115.0.

The dialkyl oxazolidinediones, with the two exceptions noted below, were prepared from the proper α-disubstituted glycolic acid ester by the same procedure as described above. The final products were purified either by distillation under reduced pressure or by recrystallization from petroleum ether or both. Yields averaging 80% were obtained. The physical characteristics of these compounds, together with their anesthetic activities and toxicities, are given in Table II.

5-*t*-Butyl-5-methyl-2,4-oxazolidinedione.—A mixture composed of 14.5 g. of α-*t*-butyl-α-methylglycolamide, 15 cc. of ethyl chlorocarbonate and 25 cc. of toluene was refluxed in an oil-bath for three hours, at which time the evolution of hydrogen chloride had nearly ceased. The condenser was arranged for downward distillation and the bath temperature raised slowly to 150°. After all the volatile material had distilled off, the reaction mixture was cooled and stirred with 100 cc. of a 10% solution of sodium carbonate. The small amount of oil remaining was extracted with ether and the aqueous portion acidified with hydrochloric acid. This precipitated the product as a colorless solid. The yield of pure material in this case amounted to 10 g. (65%) but was much lower when other amides were used. Diisopropyloxazolidinedione was prepared in 50% yield in the same way from α-diisopropylglycolamide.

Summary

A method has been developed for the preparation of 5-substituted-2,4-oxazolidinediones by the condensation of an α-hydroxy ester with urea in the presence of sodium ethylate. Nineteen new dialkyl derivatives have been prepared and characterized. These substances were found to exhibit hypnotic action, and their relative anesthetic activity in white mice has been evaluated.

NASHVILLE, TENNESSEE RECEIVED MAY 27, 1941

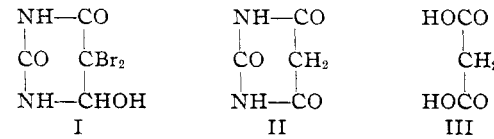
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Action of Dibromoxyhydrouracil on Malonic and Barbituric Acids[1]

BY TREAT B. JOHNSON[2] AND MARY G. WINTON

The two reactions, which the authors describe in this paper, serve to illustrate the dual reactivity inherent in the pyrimidine dibromoxyhydrouracil (I): namely, (1) its ability to donate bromine to an organic compound and (2), to serve as an oxidizing agent in aqueous and non-aqueous solutions. Experimentation with other representatives of this series of hydropyrimidines promises to be productive of results of equal interest to those brought about by interactions with the pyrimidine (I).

As is well known, malonic acid (III) and barbituric acid (II) are subject to several chemical reactions in common, due to the presence of the reactive methylene group (—CH_2—) functioning in their respective molecules. It was, therefore, of special interest to the authors to investigate the comparative behavior of these two reagents toward dibromoxyhydrouracil (I).



Malonic acid (III) and barbituric acid (II) both interact immediately when heated with dibromoxyhydrouracil (I) in aqueous solution with production of compounds already described in the literature. In both reactions the dihydro-

(1) Researches on Pyrimidines, CLXXIV.

(2) One unit of a research program partially supported by a grant from the George E. Sheffield Research Fund of the Sheffield Scientific School.