[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

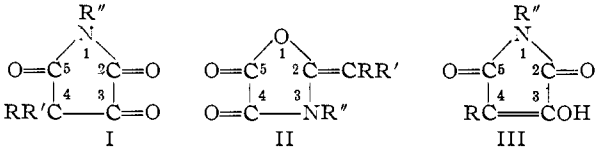
Synthesis and Properties of Oxazolidinediones and Pyrrolidinetriones

BY GLENN S. SKINNER AND RICHARD E. LUDWIG

RECEIVED DECEMBER 19, 1955

Trialkylpyrrolidine-2,3,5-triones have now been prepared by rearrangement of the 3-alkyl-2-dialkylmethyleneoxazolidinediones in alcohol solutions. Under these conditions the 3-alkyl-2-monoalkylmethyleneoxazolidinedione rearranges to the hydroxymaleimide. Similar treatment of the 2-monoalkyl- or 2-dialkylmethyleneoxazolidinedione causes cleavage to the corresponding amide. A comparative study of the preparation, properties and structure of these compounds has been made.

1,4,4-Trialkylpyrrolidine-2,3,5-triones (I) of proved structure have not been reported. 1,4-Diphenyl-4-ethylpyrrolidine-2,3,5-trione[1] was prepared incidentally from the corresponding oxazolidinedione (II) due to the fact that the latter had been crystallized from ethyl alcohol, a procedure which results in the rearrangement of II to the trialkylpyrrolidinetrione. The previously prepared pyrrolidinetriones[2] bearing a hydrogen at position 4 are tautomers which give reactions for both ketones and enols. We have also shown[3] that the cyclization of ethyl α-cyano-β-hydroxycinnamate and the condensation of ethyl oxalate with phenylacetamide under basic conditions yield the identical 4-phenylhydroxymaleimide. The attempt to form this compound by rearrangement of 2-benzylideneoxazolidinedione in alcohol resulted in cleavage to phenylacetanilide.



I II III

In this paper we report the preparation of 1,4,4-trialkylpyrrolidine-2,3,5-triones (I) in almost quantitative yield by the rearrangement of the corresponding 3-alkyl-2-dialkylmethyleneoxazolidinediones (II) in alcohol; see Table I. 2-Benzylideneoxazolidinedione,[3] however, was cleaved to the amide by refluxing with absolute alcohol. Likewise, we found that the 2-dialkylmethyleneoxazolidinediones, X, XI and XII (Table I), are cleaved to the amides under these conditions; XII also yielded the amide when treated with alcohol at room temperature. It would therefore appear that if a hydrogen atom is linked to the nitrogen, rearrangement of the oxazolidinedione to the pyrrolidinetrione will not occur under these conditions. When 2-benzylidene-3-phenyloxazolidinedione (XIII) was refluxed with absolute alcohol, both the maleimide XV and the amide were obtained; this rearrangement was studied under a variety of conditions, the details of which are reported in the Experimental section.

The oxazolidinediones listed in Table I were prepared by the condensation of N-alkylacetamides with oxalyl chloride. The oxazolidinediones slowly decompose unless they are carefully purified and kept dry; those containing aromatic groups are more stable than those containing aliphatic groups.

We have continued our attempt to prepare pyrrolidinetriones by the sodium ethoxide condensation of amides with ethyl oxalate[3]; phenylacetanilide gave 1,4-diphenylhydroxymaleimide (III). However, the introduction of a second group at the α-carbon prevented the condensation to I in which R and R′ would be alkyl groups and R″ either an alkyl group or hydrogen. For example, when α-phenylbutyranilide was treated with sodium ethoxide (or even with the stronger bases, potassium ethoxide and triphenylmethyl) the amide was recovered quantitatively. α-Phenylbutyramide likewise gave only the starting material.

Triphenylpyrrolidinetrione (with two phenyl groups in position 4) was cleaved to the amide by sodium ethoxide. Unlike the highly acidic 1,4-diphenylhydroxymaleimide, this compound cannot accommodate the sodium ion or neutralize the ethoxide ion. The less acidic amide cleavage product has the greater capacity to do so and it is not surprising that the reaction in this case proceeds toward the amide rather than the pyrrolidinetrione.

The pyrrolidinetriones, in general, have lower melting points (Table I) and have a paler yellow color than the corresponding oxazolidinediones. However, 1,4-diphenylhydroxymaleimide (XV) is more deeply colored than the corresponding oxazolidinedione (XIII).

Color reactions with bromine and with permanganate can be used to distinguish these two classes of compounds. All of the oxazolidinediones and 1,4-diphenylhydroxymaleimide (XV) reacted with permanganate in acetone; none of the trialkylpyrrolidinetriones decolorized this reagent even after 1.5 hr. Oxazolidinediones with only phenyl groups linked to the methylene carbon did not react with bromine in carbon tetrachloride, but those with ethyl groups at the methylene carbon reacted rapidly; the trialkylpyrrolidinetriones and XV did not decolorize this reagent even after standing for 24 hr. The trialkylpyrrolidinetriones gave an immediate and permanent orange color with cold, freshly distilled aniline, while the lemon-yellow color from the oxazolidinediones faded with time.

The infrared absorption data of isomers (Table II) disclose that characteristic absorption bands of the oxazolidinediones occur at 5.55, 5.80 and 5.98 μ. The corresponding trialkylpyrrolidinetriones have two bands at 5.65 and 5.90 μ. The oxazolidinediones which are unsubstituted on the nitrogen have a strong band at 3.20 μ in addition to the three characteristic bands.

Corresponding oxazolidinediones and pyrrolidinetriones gave quantitative yields of identical amides

(1) G. S. Skinner and J. F. Perkins, THIS JOURNAL, **72**, 5569 (1950).

(2) (a) R. Stolle and M. Luther, *Ber.*, **53**, 314 (1920); (b) J. C. Sheehan and E. J. Corey, THIS JOURNAL, **74**, 360 (1952); (c) V. Harlay, *J. pharm. chim.*, **24**, 537 (1936).

(3) G. S. Skinner and C. B. Miller, Jr., THIS JOURNAL, **75**, 977, 6359 (1953).

TABLE I

Oxazolidine-4,5-diones								Corresponding pyrrolidinetriones				2,4-Dinitrophenylhydrazones[l]		
No.	R	R′	R″	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found	No.	M.p., °C.	Nitrogen, % Calcd.	Found	M.p., °C.	Nitrogen, % Calcd.	Found
IV	$C_6H_5CH_2$	C_6H_5	C_6H_5	85	150–151	3.94[m]	3.80	XVII	134–135	3.94[p]	4.18			
V	C_6H_5	C_2H_5	C_6H_5	79	135–136[a]	4.78[n]	4.95	XVIII	116–117[b]	4.78[q]	5.10	196–197	14.80	14.94
VI	C_6H_5	C_6H_5	C_2H_5	76	165–166[c]			XIX	93–94	4.78[r]	4.67	209–210	14.80	15.02
VII	C_6H_5	C_6H_5	CH_3	92	235–236	5.02	5.20	XXII	138–139	5.02	5.00	250–251	15.24	15.48
VIII	C_2H_5	C_2H_5	C_6H_5	82	70–71[d]			XX	60–61	5.71	5.70	180–181	16.48	16.85
IX	C_2H_5	C_2H_5	C_2H_5	62	150[e]			XXI	Liq.[f]	[g]	[g]	149–150	18.55	18.56
X	C_6H_5	C_2H_5	H	75	125–126	6.46	6.38							
XI	C_2H_5	C_2H_5	H	78	85–86	8.28	8.24							
XII	C_6H_5	C_6H_5	H	91	159–160[h]									
XIII	C_6H_5	H	C_6H_5	86	239–240[i]			XV[j]	197–198	5.28	5.30			
XIV	C_6H_5	C_6H_5	C_6H_5	99	232–233[k]			XVI	172–173	4.11[s]	4.04	272–273	13.42	13.30
XXIII	$CH_2(CH_2CH_2-)_3$		C_6H_5	72	133–134	5.45	5.40	XXIV	181–182	5.45	5.20	238–239	16.00	15.64

Ref. 1 reports m.p., °C.: [a] 129–130°; [b] 114.5–115.5°; [c] 164–165°; [d] 46–48°; [h] 159–160°; [i] 239–240°; [k] 232–233°. [e] B.p. 1.3 mm., ref. 1: 151–153° (4.4 mm.). [f] B.p. 93–95° (0.6 mm.). [g] Calcd.: C, 60.9; H, 7.7. Found: C, 60.4; H, 7.7. [j] Hydroxymaleimide. [l] All of the 2,4-dinitrophenylhydrazones were crystallized from ethyl acetate. [m] Calcd.: C, 77.74; H, 4.82. Found: C, 77.65; H, 4.78. [n] Calcd.: C, 73.71; H, 5.16. Found: C, 73.60; H, 5.05. [p] Calcd.: C, 77.74; H, 4.82. Found: C, 77.86; H, 4.86. [q] Calcd.: C, 73.71; H, 5.16. Found: C, 73.80; H, 5.17. [r] Calcd.: C, 73.71; H, 5.16. Found: C, 73.71; H, 5.23. [s] Calcd.: C, 77.41; H, 4.43. Found: C, 77.52; H, 4.51.

TABLE II

INFRARED ABSORPTION SPECTRA[a] OF ISOMERS

Oxazolidinedione					Pyrrolidinetrione		
XIV		5.62	5.82	6.07	XVI	5.68(w)	5.88
IV		5.55	5.78	6.01	XVII	5.67(sh)	5.85
V		5.57	5.80	6.00	XVIII	5.66(sh)	5.85, 5.93(sh)
VI		5.53	5.83	6.08	XIX	5.65(sh)	5.85(sh), 5.90
VIII		5.58	5.82	5.98	XX	5.70(sh)	5.90
IX		5.50	5.80	5.95	XXI	5.63(sh)	5.84, 5.90, 5.96
VII		5.52	5.78	6.09	XXII	5.60(sh)	5.70(sh), 5.86
XXIII		5.53	5.78	5.96	XXIV	5.65	5.85, 5.92(sh)
XII	3.20	5.50	5.83	6.02			
X	3.20	5.52	5.80	5.98(sh)			
XI	3.17	5.43	5.53(sh)	5.80			
1,4-Diphenylhydroxymaleimide					3.2	5.7	6.0
1-Phenyl-3-phenylaminomaleimide					3.02	5.69	5.9
1,4-Diphenyl-3-phenylaminomaleimide					3.02	5.69	5.9

[a] The infrared data were obtained under the supervision of Dr. H. C. Beachell. (w), weak; (sh), shoulder.

when refluxed with potassium hydroxide in alcohol; both were stable in boiling dry acetic acid.

The degradation of these compounds was carried out by treatment with aniline and by ozonolysis. The pyrrolidinetriones having one or two ethyl groups at position 4 were not cleaved when treated with aniline at 185°, while one containing two phenyl groups at this position was cleaved to the amide. 2-Benzylideneoxazolidinedione reacted with cold aniline to give N-phenyl-N′-phenylacetyloxamide[4] with cleavage at position 5. Its N-phenyl derivative XIII, however, was split to oxanilide and phenylacetanilide, and the oxazolidinediones (XII and XIV) likewise gave oxanilide and the corresponding diphenylacetamide or diphenylacetanilide; cleavage of the oxazolidine ring in these cases occurs, therefore, at both positions 3 and 5.

The ring structure and location of the double bond is further established by the fact that oxazolidinedione VI gave benzpinacol by decomposition of the ozonide in the presence of zinc. The other moiety of the molecule was decomposed by calcium hydroxide to calcium oxalate and ethylamine. The ozonide from IX, similarly decomposed, gave diethyl ketone; the remaining product of the reaction has not been obtained in a pure state. The comparable pyrrolidinetrione XXI did not react with ozone. 1,4-Diphenylhydroxymaleimide underwent ozonolysis to give a 70% yield of phenylglyoxylanilide.

1,4-Diphenyl-3-phenylaminomaleimide has been prepared and the position of the double bond between carbon atoms 3 and 4 has been established by ozonolysis to oxanilide.

The pharmacological screening tests[5] on the pyrrolidinetriones indicate that only the triethyl derivative XXI has significant anticonvulsant properties.

Experimental

Amides.—The N-alkylacetamides were made by the interaction of the appropriate acid chloride and amine in benzene as previously described.[1] Yields of more than 90% also were obtained by the dropwise addition of the acid chloride (1 mole) in 200 cc. of ether to 3 moles of ice-cold aqua ammonia (sp. gr., 0.90) with stirring. α,β-Diphenylpropion-

(4) Identified by its hydrolysis to oxanilic acid and phenylacetamide.

(5) Made by Eli Lilly and Co.

anilide (yield 92%; m.p., 170–171°) has not previously been reported.

Anal. Calcd. for $C_{21}H_{19}ON$: C, 83.64; H, 6.35; N, 4.65. Found: C, 83.85; H, 6.45; N, 4.46.

4,5-Oxazolidinediones (Table I).—These compounds were prepared by the condensation of N-alkylacetamides with oxalyl chloride.[1] In general a better product was obtained by refluxing only 15 minutes after about 90% of the calculated hydrogen chloride had been evolved.

Decomposition of 2-Diethylmethylene-3-phenyloxazolidinedione.—This sample after standing 3 years in a stoppered sample bottle was observed to have decomposed. Crystallization from ligroin gave oxanilic acid, m.p. 148–150°, identical with an authentic sample. Another portion of the material was distilled with steam. The very dilute solution of the volatile acid gave Du Claux numbers: 35.4, 27.0, 15.1. A similar solution of diethylacetic acid gave Du Claux numbers: 35.9, 27.8, 15.7. A sample of our preparation was unchanged after 51 days in a desiccator; exposed to the atmosphere, the melting point was lowered to 65–69°, and in contact with water it had changed to a gummy material, m.p. 47–51°.

Rearrangement of Trialkyloxazolidinediones to Trialkylpyrrolidinetriones.—The oxazolidinedione (0.5 g.) in 20 cc. of ethanol was refluxed gently until the yellow color of the solution faded to a constant value. The pyrrolidinetriones separated from the cooled solutions in almost quantitative yields (Table I). These compounds are relatively stable. 2-Propanol was equally satisfactory for the conversion of XIV to XVI but methanol, 1-propanol and *t*-butyl alcohol caused increasing degradation to the amide.

Attempts to Prepare 4,4-Dialkylpyrrolidinetriones by Rearrangement of 2-Dialkylmethyleneoxazolidinediones.—Three oxazolidinediones of this type were refluxed in absolute alcohol. No dialkylpyrrolidinetrione could be isolated.

No.	Wt., g.	Alcohol, cc.	Time, hr.	Amide, %	M.p., °C.
X	0.5	20	12	67	84–86
XI	0.5	20	3	79	110–111
XII	1.0	50	5	82	168.5–169

When a solution of XII (0.20 g.) in 25 cc. of alcohol was allowed to stand at room temperature (*ca.* 30°) until the color faded to a constant value, a 94% yield of the amide was obtained and no pyrrolidinetrione; similar results were obtained with methanol, 1-propanol, 2-propanol, *t*-butyl alcohol and cyclohexanol. The following reagents at gentle reflux for 39 hr. gave no amide or pyrrolidinetrione and excellent recovery of the oxazolidinedione: 0.3 g. of phenol in 20 ml. of benzene; tetrahydrofuran; dry acetic acid.

Rearrangement of 2-Benzylidene-3-phenyloxazolidinedione (XIII) to 1,4-Diphenylhydroxymaleimide (XV).—Titration of the oxazolidinedione in acetone with 0.1 *N* sodium hydroxide yielded 3.6% of 1,4-diphenylhydroxymaleimide. Titration of XIII in alcohol containing a drop of pyridine[2b] gave a yield of 43%.

A mixture of 1.0 g. (0.0038 mole) of XIII, 15 cc. of dry toluene and 1.0 g. (0.0185 mole) of sodium methoxide was shaken for 15 min. This mixture was then shaken with 10 cc. (0.12 mole) of hydrochloric acid (sp. gr. 1.19) and 10 g. of ice for 20 min. The yellow solid was filtered with suction and the toluene layer extracted with sodium bicarbonate solution. This extract combined with the sodium bicarbonate solution from the solid upon acidification gave 0.86 g. (86%) of XV as a yellow precipitate, m.p. 197–198°.

XIII did not rearrange upon refluxing with only glacial acetic acid. Therefore to 20 cc. of glacial acetic acid, that had been refluxed briefly with 1 cc. of acetic anhydride, was added 2.0 g. (0.0244 mole) of fused sodium acetate and 2.0 g. (0.00756 mole) of XIII. The refluxing mixture assumed a bright orange color in 10 minutes. After refluxing 3 hr., the cooled solution was acidified as described above; the washed, dried precipitate dissolved in the minimum amount of toluene and treated as above, yielded 0.49 g. (25%) of the hydroxymaleimide XV, m.p. 197–198°. The toluene layer, after drying with calcium chloride, deposited 1.28 g. (64%) of unchanged oxazolidinedione.

A solution of 1.0 g. of XIII in 50 cc. of absolute alcohol was refluxed for 44 hr. and the alcohol removed. The residue upon treatment with a 5% sodium bicarbonate solution gave 0.565 g. (56%) of the soluble hydroxymaleimide XV and 0.330 g. (42%) of the insoluble phenylacetanilide. When the time of refluxing was shortened to 1.5 hr., the yield of XV was 62% and only a trace of the amide was formed.

Condensation of Amides with Ethyl Oxalate.—The procedure was essentially that described for the sodium ethoxide condensation of ethyl oxalate with phenylacetamide.[3] Additional 1,4-diphenylhydroxymaleimide (XV) was obtained by the sodium bicarbonate extraction of the organic layer of the mother liquor. The total yield of XV was 77%, m.p. 197–198°.

Similar treatment of α-phenylbutyranilide and α-phenylbutyramide yielded only the starting material; an almost quantitative recovery of the anilide resulted from the similar use of potassium ethoxide with α-phenylbutyranilide.

To a solution of sodium triphenylmethyl in ether prepared from 2.88 g. (0.125 mole) of sodium was added a solution of 12.0 g. (0.050 mole) of α-phenylbutyranilide in 100 cc. of ether and 6.8 cc. (0.050 mole) of diethyl oxalate. The red solution became colorless. The ether was distilled and replaced by 200 cc. of benzene which was brought to 80° and then allowed to stand at room temperature, whereupon 1.5 g. of triphenylmethyl peroxide, m.p. 184–185°, identical with an authentic sample, separated. Stepwise concentration of the solution gave 9.6 g. of the anilide, 7 g. of triphenylmethane and no pyrrolidinetrione.

Reaction of Sodium Ethoxide with 1,4,4-Triphenylpyrrolidinetrione.—A stirred mixture of 0.41 g. (0.0060 mole) of sodium ethoxide, 25 cc. of toluene and 1.0 g. (0.0030 mole) of 1,4,4-triphenylpyrrolidinetrione was heated at 75° for 1 hr. The toluene layer from treatment of the cold mixture with an excess of dilute hydrochloric acid was washed with water, dried over calcium chloride and concentrated to yield 0.55 g. (64%) of diphenylacetanilide, m.p. 179–181°.

Qualitative Tests for Oxazolidinediones and Pyrrolidinetriones.—To a solution of 0.05 g. oxazolidinedione in 3 cc. of carbon tetrachloride was added five drops of a 5% solution of bromine in carbon tetrachloride. In a second test a solution of 0.1 g. of the oxazolidinedione in 2 cc. of acetone was treated with five drops of a 2% aqueous solution of potassium permanganate.

Reaction with Potassium Hydroxide.—Oxazolidinediones IV, V and XIV and the pyrrolidinetriones XVII, XVIII and XVI were each refluxed for 0.5 hr. in alcohol containing two equivalents of potassium hydroxide. Corresponding compounds gave excellent yields of the identical amides having melting points 170–171°, 95–96° and 180–181°, respectively.

Reaction of Aniline with Oxazolidinediones and Pyrrolidinetriones.—Each of the seven compounds (0.5 g.) listed below was heated at 185° for 15 min. with 5.0 cc. of freshly distilled aniline. The oxanilide which separated on cooling was filtered and washed with ether. The amide was isolated by removal of the ether and acidification of the cold filtrate with 10% hydrochloric acid. The products were identified by mixed melting point determinations.

Type	Compound	Oxanilide, %	Amide, %	Recovered, %
Oxazolidinedione	V	99	93	0
Pyrrolidinetrione	XVIII	0	0	92
Pyrrolidinetrione	XVI	77	95	0
Oxazolidinedione	IX	90	41	0
Pyrrolidinetrione	XXI	0	0	100
Oxazolidinedione	XII	96	93	0
Pyrrolidinetrione	XX	0	0	94

A mixture of 1.0 g. of the oxazolidinedione, 1.0 cc. of aniline and 30 cc. of tetrahydrofuran was allowed to stand[3] at room temperature for 3–4 hours with the following results.

No.	R	R′	R″	Oxanilide, %	Amide, %
XII	C_6H_5	C_6H_5	H	72	74
XIV	C_6H_5	C_6H_5	C_6H_5	82	89
XIII	C_6H_5	H	C_6H_5	70	63
	C_6H_5	H	H	N-Phenylacetyl-N′-phenyloxamide 66%[a]	

[a] Required 15 minutes.

N-Phenyl-N′-phenylacetyloxamide[3] was identified as follows: 0.7 g. (m.p. 204–205°) in 10 cc. of alcohol was treated with 1 cc. of 10% sodium hydroxide solution. The

white gelatinous precipitate was filtered, treated with dilute acid and extracted with ether. The residue from distillation of the ether was crystallized from toluene to give 0.3 g. of oxanilic acid (m.p. 152–154°) identical with an authentic sample. The white solid, from evaporation of the original filtrate, upon recrystallization from alcohol gave 0.18 g. of phenylacetamide.

1,4-Diphenyl-3-phenylaminomaleimide.—1,4-Diphenylhydroxymaleimide (10 g., 0.0378 mole) mixed with 45 cc. of aniline was heated at 185° for 0.5 hr. The cold, dark brown solution was poured with stirring into 500 cc. of water containing a large excess of hydrochloric acid. The bright yellow precipitate was filtered and crystallized from hot alcohol to give fine yellow needles, 12.1 g. (94%), m.p. 209–210°.

Anal. Calcd. for $C_{22}H_{16}O_2N_2$: N, 8.24. Found: N, 8.14.

Ozonolysis.—A standard procedure[6a–c] using a Welsbach-T-25 ozonator was adopted for our purpose. 2-Diethylmethylene-3-ethyloxazolidinedione (IX) (19.7 g., 0.10 mole) dissolved in 80 cc. of glacial acetic acid was treated in the gas dispersion tube with a current of O_3–O_2 until ozone was detected at the outlet. The ozonide was carefully added dropwise to a stirred, boiling mixture of 250 cc. of water, 30 g. of zinc dust, 0.10 g. of silver nitrate and 0.055 g. of hydroquinone over a period of 2 hr. and 20 min. The refluxing was continued for one hr. The Dry Ice trap contained 1.5 g. of diethyl ketone. The reaction mixture was filtered by gravity and the filtrate was distilled with steam. From the steam distillate there was obtained 3 g. of diethyl ketone by extraction with ether and 1.0 g. by precipitation as the 2,4-dinitrophenylhydrazone (m.p. 156–157°); this accounts for 64% of the theoretical amount. The zinc was removed by precipitation as zinc sulfide. Distillation of the filtrate under diminished pressure left 6.2 g. of a greasy solid, b.p. 95–105° (0.65 mm.), m.p. 108–112°. It resisted purification.

(6) (a) C. R. Noller and Roger Adams, THIS JOURNAL, **48**, 1074 (1926); (b) F. C. Whitmore and J. M. Church, *ibid.*, **54**, 3710 (1932); (c) J. M. Church, F. C. Whitmore and R. V. McGrew, *ibid.*, **56**, 176 (1934).

A solution of 10 g. (0.0342 mole) of 2-diphenylmethylene-3-ethyloxazolidinedione (VI) in 60 cc. of glacial acetic acid was subjected to ozonolysis. A considerable amount of pale yellow solid (5 g.) was filtered with the zinc dust; this material dissolved in ether. Recrystallization from carbon tetrachloride gave 4.2 g. of benzpinacol, m.p. 192–194° (rapid heating) equivalent to 0.023 mole (67%) of benzophenone; admixture with an authentic sample caused no depression of the m.p.; when it was added to a concentrated solution of sodium ethoxide, a bright blue color was obtained. The above filtrate after removal of the zinc with hydrogen sulfide, yielded 2.2 g. (50%) of calcium oxalate upon treatment with calcium hydroxide. This treatment caused the evolution of ethylamine.

Under similar conditions 1,4,4-triethylpyrrolidinetrione did not react with ozone.

A solution of the ozonide from 10.0 g. (0.0377 mole) of 1,4-diphenylhydroxymaleimide (XV) in 100 cc. of glacial acetic acid was added dropwise with stirring to 200 cc. of water at 5° in the course of 1 hr. After 2 hr. at room temperature the mixture was concentrated under diminished pressure to 16 g. The residue was dissolved in ether and extracted repeatedly with water. The residue from the distillation of the ether was dissolved in alcohol and treated with Darco. The filtrate was diluted with an equal volume of water to give 6.0 g. (70%) of phenylglyoxylanilide, m.p. 62–63°. This was identical with an authentic sample prepared from mandelic acid. The yield of calcium oxalate from the above aqueous extract was 2.9 g. (60%).

A solution of the ozonide from 10.0 g. of 1,4-diphenyl-3-phenylaminomaleimide was similarly decomposed to give, after recrystallization from toluene, 5.2 g. (72%) of oxanilide; m.p. and mixed m.p. 249–250°. The aqueous acetic acid solution was concentrated under diminished pressure and toluene was added until the distillate consisted only of toluene. The water extract from the dark residue was extracted with ether. Evaporation of the ether left 2 g. of gummy material which resisted purification. Extraction of the toluene layer with sodium bicarbonate solution led to the isolation of 1.2 g. of benzoic acid. No phenylglyoxylic acid could be detected.

NEWARK, DELAWARE

[CONTRIBUTION FROM THE SCHOOL OF SCIENCE, BRANDEIS UNIVERSITY]

New Nitrogen Mustards for "Toxagenic" Anti-cancer Agents[1a,b]

BY ORRIE M. FRIEDMAN AND ELIAHU BOGER

RECEIVED JANUARY 21, 1956

Two new secondary amine mustards, 5-chloro-1-(chloromethyl)-*n*-pentyl-2-chloroethylamine hydrochloride (V) and 6-chloro-1-(chloromethyl)-*n*-hexyl-2-chloroethylamine hydrochloride (VI), capable of intramolecular cyclization to potent tertiary amine mustards VII and VIII, respectively, have been synthesized. While both were phosphorylated with phosphorus oxychloride the latter VI, the more toxic of the two, appears ideal for the preparation of toxagenic phosphamides for use against tumors in which phosphamidase or functionally related enzymes may be found. The former V appears insufficiently toxic.

One of the promising approaches to cancer chemotherapy is based upon the use of toxagenic substrates—substances from which highly cytotoxic agents would be liberated by the action of enzymes.[2a–f] Advantage of a favorable distribution of an enzyme in a tumor might be taken, for example, by the use of a toxagenic substrate that would be acted upon by the enzyme to liberate a cytotoxic agent intracellularly. In this way a lethal dose of a cytotoxic agent might be delivered to the cells of the tumor whereas a relatively smaller, non-lethal dose would reach the cells of normal tissues in which less of the enzyme was present. This report describes the synthesis of two new nitrogen mustards of interest for the synthesis of toxagenic agents for use against malignant tumors in which the enzyme ahosphamidase[3a–g] or functionally related enzymes may be found.[2b]

(1) (a) This investigation was supported by a research grant from the National Cancer Institute of the National Institutes of Health, Department of Health, Education and Welfare, U. S. Public Health Service. (b) Presented in part at the 128th meeting of the American Chemical Society, Minneapolis, September, 1955.

(2) (a) O. M. Friedman and A. M. Seligman, THIS JOURNAL, **70**, 3082 (1948); (b) **76**, 655 (1954); (c) **76**, 658 (1954); (d) A. M. Seligman, M. M. Nachlas, L. H. Manheimer, O. M. Friedman and G. Wolf, *Ann. Surg.*, **130**, 333 (1949); (e) A. M. Seligman, M. Milden and O. M. Friedman, *Cancer*, **2**, 701 (1949); (f) A. M. Rutenberg, L. Persky, O. M. Friedman and A. M. Seligman, *J. Pharm. Exp. Therap.*, III, 483 (1954).

(3) (a) M. Ichihara, *J. Biochem. (Japan)*, **18**, 87 (1933); (b) E. Waldschmidt-Leitz, *Biochem. Z.*, **258**, 360 (1933); (c) H. Bredereck and E. Ceyer, *Z. physiol. Chem.*, **254**, 223 (1938); (d) G. Gomori, *Proc. Soc. Exp. Biol. Med.*, **69**, 407 (1948); (e) E. H. Strecker, *Dent. Med. Wochschr.*, **74**, 1268 (1951); (f) L. A. Tseitlin, *Biokhimiya*, **17**, 208 (1952); (g) J. Meyer and J. Weinman, *J. Dent. Res.*, **32**, 669 (1953).