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SOME MACROCYCLIC OXALACTONES AND RELATED SUBSTANCES

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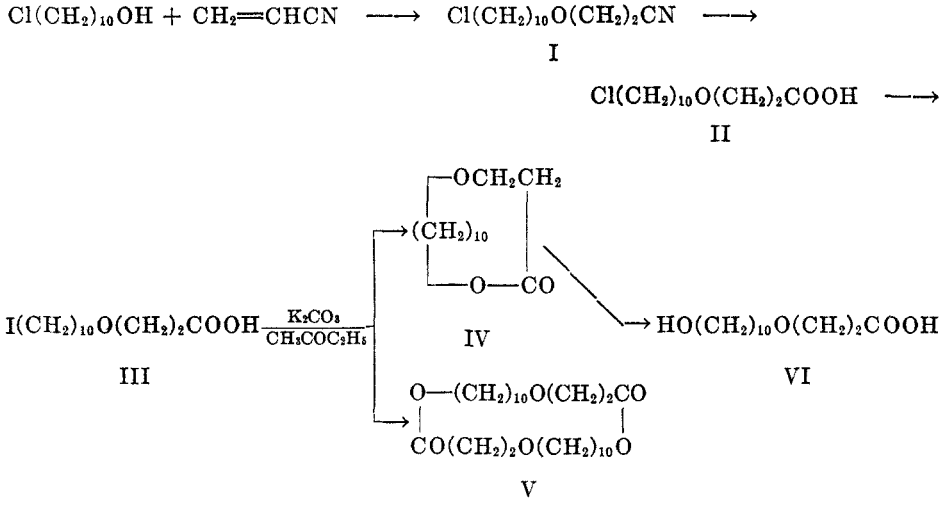
Many macrocyclic ketones and lactones are very useful to the perfumer on account of their musklike odor. The synthesis of even the most accessible is fairly complicated, the lactones, as a rule, being less readily obtainable (1). It is not essential that all ring members of the cyclic ketones be carbon atoms,[1] nor that the heterocyclic lactones have only one oxygen atom in the ring. In this paper there are described the preparations of lactones having several hetero atoms and of a possible intermediate for a heterocyclic ketone.

Decamethylene chlorohydrin (2) adds to acrylonitrile to give 14-chloro-4-oxatridecanonitrile (I), which is easily hydrolyzed to the corresponding acid (II). On treatment with sodium iodide in acetone, the chloro acid is converted to the iodo acid (III). The latter is then cyclized to the 15-membered lactone (IV) of 14-hydroxy-4-oxatetradecanoic acid in a yield of 76%, following Hunsdiecker's procedure (3).



The infrared spectra[2] of lactone IV and Exaltolide (cyclopentadecanolide) are compared in Fig. 1. The close similarity is obvious; the major differences occur in the region of the ether linkages.

A dimeric lactone (V) having thirty ring members was also formed, and isolated, in a yield of 1%. These lactones are isomeric with others described in the

[1] Moncrieff (4) gives an excellent review of the syntheses and properties of ether-lactones. See also Moncrieff, "The Chemical Senses," John Wiley & Sons, Inc., New York, pp. 210–215 (1946).

[2] We are indebted to Mr. William Blum, of Distillation Products, Inc., for these data. The thickness of the layer is 0.005 inch.

literature (5, 6). The new monomeric lactone was hydrolyzed to 14-hydroxy-4-oxatetradecanoic acid (VI); it belongs to a general type included in a patent of Firmenich et Cie (7).

The corresponding properties of the two monomeric lactones are compared in Table I.

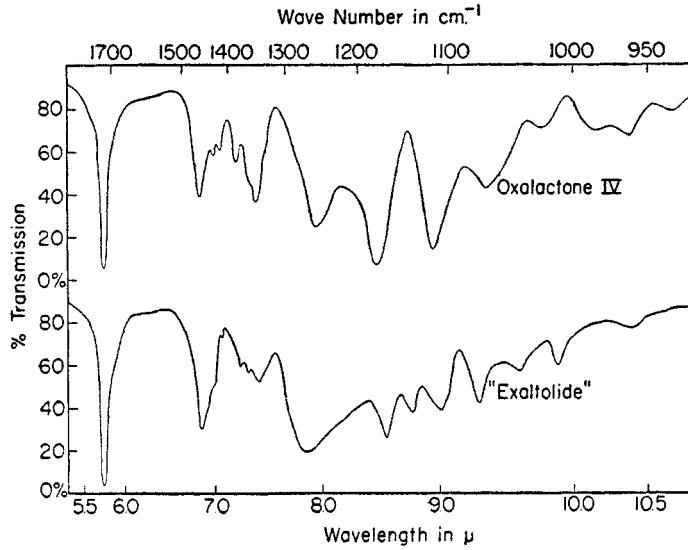


FIG. 1. INFRARED SPECTRA OF OXALACTONE (IV) AND OF EXALTOLIDE

TABLE I

PHYSICAL PROPERTIES OF ISOMERIC OXALACTONES

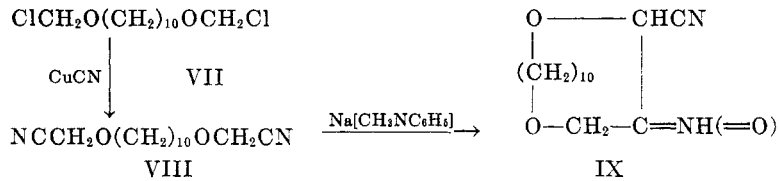
LACTONE FROM	M.P., °C.	B.P., °C.	d_4^{25}	n_D^{26}	MOL. REFR.		
					Obs.	Calc'd	Diff.
14-Hydroxy-4-oxatetradecanoic acid	1.5	135–137/2 mm.	1.012	1.4670	62.54	63.33	−0.79
14-Hydroxy-12-oxatetradecanoic acid (6)	8.0	108–111/1 mm.	0.9916[a]	1.4645[a]	63.52	63.39	+0.13

[a] Temp., 33°.

The monomeric oxalactone (IV) has a fine, sweet odor, resembling that of Exaltolide.

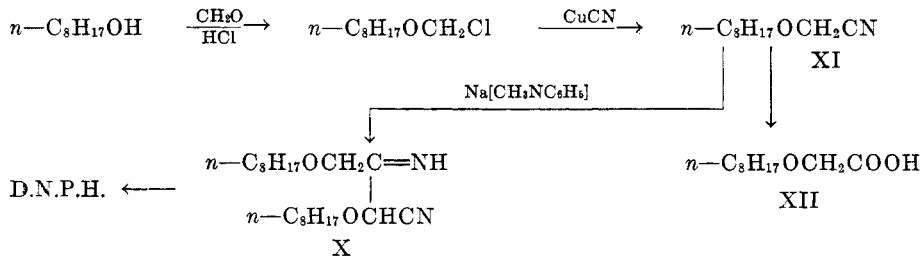
A different approach to the many-membered heterocyclic ketones also starts with decamethylene glycol, which is easily converted to decamethylenedioxymethyl chloride (VII) by means of formaldehyde and hydrogen chloride (8). The chloride reacts with cuprous cyanide (9) to give decamethylene-1,10-dioxymethyl cyanide (VIII). This dinitrile is then cyclized by Ziegler's high-dilution technique (10) to the iminonitrile (IX). The cyclic imine in an acidic

solution gave a 2,4-dinitrophenylhydrazone and a nictazone.[3] It appears that the imino group is hydrolyzed off as anticipated. Attempted hydrolysis of the ketonic nitrile was not successful, complete decomposition taking place; there was no musklike odor at any time. The only recognizable product was decamethylene glycol.



For purposes of comparison, an attempt was made to cyclize 1,16-dicyano-3,14-dioxahexadecane, $NC(CH_2)_2O(CH_2)_{10}O(CH_2)_2CN$ (11, 12), by the same procedure; surprisingly, it resulted mainly in *beta* cleavage, a 90% recovery of decamethylene glycol being obtained.

Because of the unexpected difficulty in the hydrolysis of the imino group of IX, a model compound, 12-cyano-9,13-dioxaheneicosanimide-11 (X) was prepared, as shown below in the outline, with a view to determining the optimum conditions for acid hydrolysis. However, extensive decomposition occurred in all attempts; the only recognizable product was *n*-octyl alcohol. The imine did give a 2,4-dinitrophenylhydrazone, like its cyclic analog.



The octyloxynitrile (XI), on the contrary, was very stable, being readily hydrolyzed to the octyloxyacid (XII) in both alkaline and acid solution.

EXPERIMENTAL

14-Chloro-4-oxatridecanonitrile (I). Acrylonitrile (29 g.) was slowly added to a well-stirred mixture of 96 g. of decamethylene chlorohydrin, 50 ml. of dioxane, and 1 ml. of trimethylbenzylammonium hydroxide, the temperature being kept below 38°. After it had been stirred for two hours at room temperature, the reaction mixture was poured into water, acidified by acetic acid, and extracted with ether. After removal of the solvent from the dried solution, the residual oil was distilled; 17.5 g. of forerun (up to 170°) was followed by the main fraction (82 g., 70%); b.p. 170–174°/5 mm.; n_D^{26} 1.458.

Anal. Calc'd for $C_{13}H_{24}ClNO$: N, 5.7. Found: N, 5.6.

[3] N-Methyl-β-carbohydrazidopyridinium *p*-toluenesulfonate is an excellent reagent for use in the identification of carbonyl compounds (16), but the name is too lengthy for convenience. Dr. F. P. Pingert, formerly of these Laboratories, proposed that the reagent be called "Nictazine," and the derivatives, "Nictazones."

14-Chloro-4-oxatetradecanoic acid (II). A mixture of 40 g. of the chloronitrile, and 100 ml. each of acetic and hydrochloric acids, was refluxed for five hours; the initially clear solution soon became turbid. It was then poured into 250 ml. of water and extracted with two 350-ml. portions of ether. After drying, the solvent was evaporated, leaving 36.5 g. (86%) of crystalline acid; m.p. 33–35°. The analytical sample was recrystallized from petroleum ether; m.p. 36–37°.

Anal. Calc'd for $C_{13}H_{25}ClO_3$: C, 59.0; H, 9.6.

Found: C, 58.9; H, 9.5.

The corresponding amide resulted when the nitrile (2 g.) was dissolved in 10 ml. of conc'd sulfuric acid at −10° and allowed to stand overnight, followed by dilution, filtration, and solution in ethylene chloride. A sodium carbonate wash ensured the absence of traces of acid. The yield was 1.8 g. (84%). The analytical sample was recrystallized from ligroin; m.p. 81–82°.

Anal. Calc'd for $C_{13}H_{26}ClNO_2$: C, 59.4; H, 9.9.

Found: C, 59.5; H, 10.1.

14-Iodo-4-oxatetradecanoic acid (III). A mixture of 36.5 g. of the chloro acid and 23.1 g. of sodium iodide in 300 ml. of acetone was refluxed for 48 hours; 7.1 g. of salt separated. After removal of the solvent, the residue was triturated with 250 ml. of water, the insoluble portion collected on a filter, and then dissolved in ether. On spontaneous evaporation of the dried solution, the iodo acid crystallized in a yield of 33 g. (68%); m.p. 48–50°. Two recrystallizations from petroleum ether raised the melting point to 54°.

Anal. Calc'd for $C_{13}H_{25}IO_3$: C, 43.8; H, 7.0.

Found: C, 43.7; H, 7.0.

Lactone (monomeric) of 14-hydroxy-4-oxatetradecanoic acid (IV). The cyclization was accomplished in a high-dilution apparatus, modified as shown in Fig. 2. A, B, and C are female standard-taper 24/40 ground-glass joints; E is a similar male joint. Two dilution wells (D) of about 10-ml. capacity are placed under the joints A and B, above which are attached efficient reflux condensers, protected from moisture, each with a drip tip, so that the condensate drops into the wells. A 300-ml. Hershberg dropping-funnel (14) is attached to C. The reaction flask, attached at E, is of suitable size, and is heated by a Glas-Col mantle. This apparatus is much more compact and less complicated than that previously used for high-dilution reactions.

A typical run was carried out as follows: In the flask were placed 200 g. of potassium carbonate and 3 l. of dry methyl ethyl ketone; the solvent was heated so as to maintain vigorous refluxing in both condensers. A solution of 71 g. of 14-iodo-4-oxatetradecanoic acid in 300 ml. of dry methyl ethyl ketone was added from the Hershberg funnel over a period of 48 hours. The cooled reaction mixture was then filtered, and the solvent evaporated; when the volume had been reduced to about 200 ml., 3.1 g. of white crystals of the dimeric lactone (V) separated, and were collected by filtration. Concentration of the filtrate to about 75 ml., followed by the addition of 50 ml. of petroleum ether gave a little more of the solid. This was removed and the residual oil fractionated *in vacuo*: 1st fraction (5 g.), b.p. up to 75°/2 mm., n_D^{30} 1.4340; 2nd (7 g.), 75–170°/2 mm., n_D^{30} 1.4410; 3rd (36 g.), 130–140°/2 mm., n_D^{30} 1.4650. The last fraction was redistilled; the portion which was collected had b.p. 135–137°/2 mm., n_D^{30} 1.4650 (n_D^{27} 1.4670); freezing point, 1.5°.

Anal. Calc'd for $C_{13}H_{24}O_3$: C, 68.4; H, 10.5; Mol. wt., 228.

Found: C, 68.8; H, 10.4; Mol. wt. (boiling C_6H_6), 224.

Dimeric lactone: 2,17-Diketo-1,5,16,20-tetraoxatriacontane (V). The solid isolated from the solution of the monomer was recrystallized from methanol; m.p. 118–119°.

Anal. Calc'd for $C_{26}H_{48}O_6$: C, 68.4; H, 10.5; Mol. wt., 456.

Found: C, 68.5; H, 10.3; Mol. wt. (in boiling C_6H_6), 464.

14-Hydroxy-4-oxatetradecanoic acid (VI). A mixture of 2 g. of the lactone, 10 ml. of water, and 5 ml. of 5% sodium hydroxide solution was heated on the steam-bath for two hours; the reaction mixture was nearly solid the next day. Water was added (about 60 ml.) to give a clear solution when heated on the steam-bath, Norit added for decolorizing, and, after

filtration, 15 ml. of conc'd hydrochloric acid was added. The precipitated oil soon crystallized; it was recrystallized from toluene; 1.4 g., m.p. 61–62°.

Anal. Calc'd for $C_{13}H_{26}O_4$: C, 63.4; H, 10.6.

Found: C, 63.7; H, 10.8.

The *acid hydrazide*, m.p. 116–117°, was obtained in the usual way from the monomeric lactone and 85% hydrazine hydrate. It crystallizes well from alcohol or ligroin.

Anal. Calc'd for $C_{12}H_{26}N_2O_3$: C, 58.5; H, 10.6.

Found: C, 58.8; H, 10.5.

1,16-Dicyano-3,14-dioxahexadecane was found to crystallize from ligroin (b.p. 90–120°), whereas in the literature (11, 12) it is described as an oil. It melts at 44–45°.

Anal. Calc'd for $C_{16}H_{28}N_2O_2$: N, 10.0. Found: N, 9.9.

1,14-Dichloro-2,13-dioxatetradecane, decamethylenedioxymethyl chloride (VII). A mixture of 100 g. of decamethylene glycol, 35 g. of paraformaldehyde ("trioxymethylene"), and 1

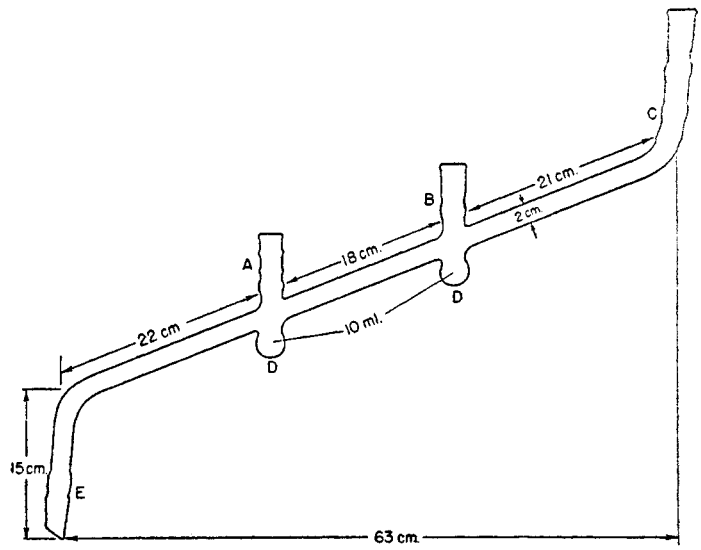


FIG. 2. HIGH-DILUTION MIXER

l. of benzene was saturated with hydrogen chloride at 5–10°; all the solid had gone into solution after four hours (8). The benzene layer was separated and distilled. The chloride boils at 200–203°/15 mm.

Anal. Calc'd for $C_{12}H_{24}Cl_2O_2$: Cl, 26.3. Found: Cl, 26.0.

1,14-Dicyano-2,13-dioxatetradecane (VIII). To a rapidly-stirred suspension of 50 g. of cuprous cyanide in 114 ml. of toluene, 67.5 g. of the chloride (VII) was slowly added. The brown solution was refluxed nine hours more, filtered, and distilled. The yield of nitrile, b.p. 219–220°/4 mm., was 87% (9, 15). It solidified on chilling, and was recrystallized from alcohol (4 ml. per g.); m.p. 33–34°.

Anal. Calc'd for $C_{14}H_{24}N_2O_2$: N, 11.1. Found: N, 10.8.

1-Cyano-4,15-dioxacyclopentadecanimide-2 (IX). The catalyst was prepared as directed in the literature (13), using 3 l. of dry ether, in dry nitrogen. When the vigorous reaction had subsided, 50.4 g. of decamethylenedioxymethyl cyanide in 500 ml. of dry ether was added over a 3-day period, using Ziegler's apparatus (10). One liter of water was added slowly, the layers separated, the ether layer was washed with dilute hydrochloric acid (170 ml. of conc'd acid diluted to 1500 ml.) to remove the methylaniline, and decanted

from a little solid. After drying and fractional distillation, 19 g. of the cyclic imide, b.p. 155–167°/1 mm., was obtained (9, 15). It was recrystallized from 50 ml. of ligroin, 18 g. being recovered. The analytical sample melted at 75–76°.

Anal. Calc'd for $C_{14}H_{24}N_2O_2$: N, 11.1; Mol. wt., 252.

Found: N, 11.1; Mol. wt. (in boiling C_6H_6), 246, 247.

Hydrolysis. A 3.4-ml. portion of conc'd sulfuric acid was diluted to 62 ml., and 15 ml. of chloroform and 2.4 g. of the cyclic imine were added; the mixture was then refluxed for two hours, the chloroform layer separated and the solvent evaporated. The residue was used directly. One portion was refluxed with methanolic potassium hydroxide, diluted, and the solid collected; it melted at 70–71° after recrystallization from ethyl acetate, and was identified as decamethylene glycol by a mixed melting point. This glycol also resulted by five hours' refluxing of the imine with hydrochloric acid.

2,4-Dinitrophenylhydrazone. This derivative was prepared from a portion of the chloroform residue above; bright yellow crystals were formed; m.p. 114–115°.

Anal. Calc'd for $C_{20}H_{27}N_5O_6$: N, 16.1. Found: N, 16.2.

Nictazone. Another portion of the chloroform residue was taken up in methanol and refluxed with Nictazine (16) for two hours. The derivative was isolated from the chilled solution and recrystallized three times from *n*-butyl alcohol; it gave yellow crystals; m.p. 242–243°.

Anal. Calc'd for $C_{28}H_{38}N_4O_6S$: C, 60.2; H, 6.8.

Found: C, 59.9; H, 6.6.

n-Octyloxymethyl cyanide; 1-cyano-2-oxadecane (XI).[4] The crude *n*-octyloxymethyl chloride, prepared in the usual way (8) from 140 g. of *n*-octyl alcohol, 1 l. of benzene, and 30 g. of paraformaldehyde, with saturation by hydrogen chloride, and separation of the benzene layer, followed by removal of the solvent, was taken up in 250 ml. of toluene. After the addition of 90 g. of cuprous cyanide, refluxing for twelve hours, filtering, and distilling, the nitrile (90 g.) was collected at 83–87°/2 mm.

Anal. Calc'd for $C_{10}H_{19}NO$: N, 8.3. Found: N, 8.1.

n-Octyloxyacetic acid (XII) was obtained by alkaline hydrolysis of the nitrile. A mixture of 25 g. of nitrile, 60 ml. of 40% aqueous sodium hydroxide, and 50 ml. of alcohol was heated on the steam-bath for fifteen hours. The alcohol was then evaporated and the residue taken up in 70 ml. of water, the solution filtered, and acidified. The acid was extracted with ether; 22 g. (79%) of crude acid remained after evaporation of the solvent. When dissolved in ligroin and chilled, the acid crystallized; it melted at about 15°. The same acid was also prepared by hydrolysis using 70% sulfuric acid for five hours.

Anal. Calc'd for $C_{10}H_{20}O_3$: C, 63.8; H, 10.6.

Found: C, 63.9; H, 10.8.

12-Cyano-9,13-dioxaheneicosanimide-11 (X)[4] was prepared essentially as described above under the cyclic imide (IX), in a yield of 88%; b.p. 206–210°/2 mm.

Anal. Calc'd for $C_{20}H_{38}N_2O_2$: N, 8.3. Found: N, 8.2.

The *2,4-dinitrophenylhydrazone*, likewise obtained as above, separated from alcohol in bright yellow plates; m.p. 43–45°.

Anal. Calc'd for $C_{26}H_{41}N_5O_6$: N, 13.5. Found: N, 13.6.

SUMMARY

Two macrocyclic oxalactones have been prepared by ring closure of suitably constituted open-chain compounds. The monomeric lactone, which has a musk-like odor, closely resembles a known isomer.

A macrocyclic dioxaimidonitrile has also been prepared. Suitable conditions for hydrolyzing the nitrogenous groups without decomposition were not found.

[4] We wish to thank Dr. Alan Bell, formerly of these Laboratories, for this preparation.

An open-chain dioxaimidonitrile was likewise degraded on hydrolysis, as was a dioxadinitrile.

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REFERENCES

(1) ALLEN, *Am. Perfumer Essent. Oil. Rev.*, **50**, 441 (1947).
(2) BENNETT AND MOSSES, *J. Chem. Soc.*, 1697 (1931).
(3) HUNSDIECKER AND ERLBACH, *Ber.*, **80**, 2129 (1947).
(4) MONCRIEFF, *Am. Perfumer Essent. Oil Rev.*, **49**, 148 (1947).
(5) SPANAGEL, U. S. Patent 2,163,109 (1939).
(6) SPANAGEL AND CAROTHERS, *J. Am. Chem. Soc.*, **58**, 654 (1936).
(7) FIRMENICH ET CIE, U. S. Patent 2,202,448 (1940).
(8) ALLEN AND VANALLAN, U. S. Patent 2,290,462 (1942).
(9) ALLEN AND VANALLAN, U. S. Patent 2,425,360 (1947).
(10) ZIEGLER, EBERLE, AND OHLINGER, *Ann.*, **504**, 122 (1933).
(11) BRUSON AND REINER, *J. Am. Chem. Soc.*, **65**, 23 (1943).
(12) BRUSON, U. S. Patent 2,437,905 (1948).
(13) ZIEGLER, German Patent 615,468 (1935); *Frdl.*, **22**, 283 (1939); *Chem. Abstr.*, **29**, 6250 (1935).
(14) HERSHBERG, *Org. Syntheses*, Coll. Vol. II, 129 (1943).
(15) ALLEN AND VANALLAN, U. S. Patent 2,388,813 (1942).
(16) ALLEN AND GATES, *J. Org. Chem.*, **6**, 596 (1941).