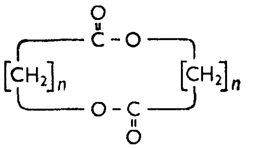
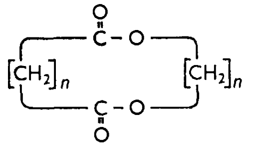
# **14.** *Macrocyclic Compounds. Part VIII.*[1] *Conformations of Symmetrical Cyclic Diesters and Dilactones.*

By Johannes Dale.

Symmetrical cyclic diesters having **10—24** ring atoms have been prepared by pyrolytic depolymerization of the corresponding polyesters. Strong dipole moment alternation in this series and, in the opposite sense, in the analogous series of dilactones is explained on conformational grounds. Infrared spectra show that the conformations are fairly rigid and unique up to the **14**-membered rings; higher members consist, in solutions, of an increasing number of conformations. A good preparative method for ω-hydroxyalkanoic acids is described.

By analogy with the two series of dilactams and symmetrical cyclic diamides studied before,[1] the corresponding series of dilactones (I) and symmetrical cyclic diesters (II)


(I)


(II)

would also be expected to show melting-point alternation, as only the members with odd *n* can have compact strain-free conformations consisting of straight parallel polymethylene chains linked by two ester bridges (Fig. 1). Those with even values of *n* must either be strained and compact (Fig. 2, a and b), or strain-free and open (Fig. 2, c and d); the resulting lack of conformational homogeneity in the melt should lead to a lower melting point.[2]

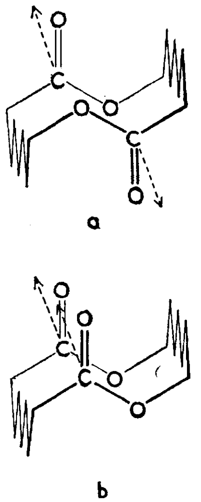


Fig. 1. Strain-free compact conformations of (a) a dilactone (I) and (b) a cyclic diester (II), both with odd $n$ $(=7)$.

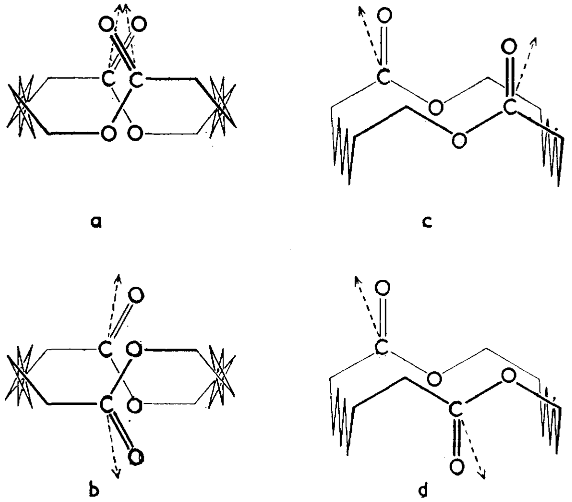


Fig. 2. Strained compact conformations (a and b) and strain-free open conformations (c and d) of a dilactone (I) (a and c) and a cyclic diester (II) (b and d), both with even $n$ $(=8)$.

Since the dipole moment of the ester group, studied extensively as a function of ring size in monolactones by Huisgen and Ott,[3] is directed nearly parallel to the C=O bond

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[1] Part VII, Dale and Coulon, *J.*, 1964, 182. (In Fig. 2 of that article the word *strained* in 2nd line of legend should read *strain-free*.)

[2] Part III, Dale, *J.*, 1963, **93**.

[3] Huisgen and Ott, *Tetrahedron*, 1959, **6**, 253.

(Figs. 1 and 2) in its most stable *trans*-configuration, a necessary consequence is also that the dilactones (I) should have the two ester dipoles oriented in opposition when $n$ is odd (Fig. 1a), and roughly parallel when $n$ is even (Fig. 2, a or c), whereas for the diesters (II) they should be parallel when $n$ is odd (Fig. 1b), and roughly in opposition when $n$ is even (Fig. 2, b or d). As discussed before,[1,2] this relative dipole orientation should accentuate melting-point alternation in the dilactone series (I) but counteract it in the diester series (II). The destabilizing effect of the parallel amide dipoles in cyclic diamides in which $n$ is odd, having *a priori* favourable conformations, has already been noted [1] as a depression of the melting points relative to those of the dilactams in which $n$ is odd. Unfortunately, the insolubility in non-polar solvents made it impossible in that case to relate the effect experimentally to differences in molecular dipole moments resulting from the relative orientation of the two amide-group moments. As the dilactones and cyclic diesters should be more soluble, it should be possible to measure their dipole moments.

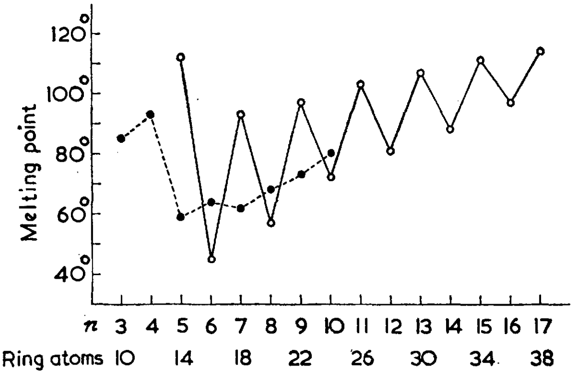

FIG. 3. Melting points of (○) dilactones (I) [4] and (●) symmetrical cyclic diesters (II).

The dilactones (I; $n = 5$—17) were first synthesized by Stoll and Rouvé,[4] who also noted the striking melting-point alternation (Fig. 3). The lower members ($n = 5$—9) were prepared for this work by the same method, but the condensation of the ω-hydroxy-alkanoic acids was carried out for shorter times and in more concentrated benzene solution, the monolactones being, in any case, unwanted. The change resulted in lower yields, but brought out a significant alternation of yield (Table 1), the conformationally more stable 18- and 22-membered rings being favoured. That the 14-membered ring does not also give the expected high yield is ascribed to especially strong competition from the 7-membered monolactone. For the preparation of ω-hydroxy acids, reported methods [5]

TABLE 1.

Yields and physical properties of dilactones (I).

| $n$ | Yield (%) * | M. p. Found | M. p. Lit.[4] | Crystal habit | $P_\infty$ (cm.$^3$) | $P_E = R_D$ (cm.$^3$) | $\mu$ (D) ($\pm$0·05 D) | $\mu_{10\%}$ (D) |
|---|---|---|---|---|---|---|---|---|
| 5 | 3 † | 112° | 112° | Thick needles | 115·0 | 59·1 | 1·65 | 1·56 |
| 6 | 5 | 45 | 41 | Hexag. thin plates | 231·0 | 68·0 | 2·82 | 2·76 |
| 7 | 25 | 92 | 93 | Thick needles | 164·8 | 77·4 | 2·07 | 1·97 |
| 8 | 4 | 57 | 57 | Thin plates | 252·9 | 94·2 | 2·79 | 2·70 |
| 9 | 10 | 96 | 97 | Thick needles | 199·2 | 94·9 | 2·26 | 2·15 |
| 10 | | 72 | 72 | Hexag. thin plates | 242·5 | 104·2 | 2·60 | 2·50 |
| 11 | | 103 | 101 | Needles | 230·2 | 113·2 | 2·39 | 2·27 |
| 14 | | 88 | 88 | Hexag. thin plates | 275·8 | 139·2 | 2·58 | 2·24 |
| 15 | | 111 | 108 | Needles | — | — | — | — |

* By condensation of 0·01M-benzene solutions. † Low yield by competition with 7-membered monolactone.

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[4] Stoll and Rouvé, *Helv. Chim. Acta*, 1935, **18**, 1087.

[5] Chuit and Hausser, *Helv. Chim. Acta*, 1929, **12**, 463.

give, in general, rather unsatisfactory yields. A very convenient procedure, giving overall yields of 50—75%, consists of treating the half-ester of a dicarboxylic acid with thionyl chloride and selectively reducing the resulting acid chloride with sodium borohydride. It was also found preferable, instead of separating the condensation product into acid and neutral fractions and isolating the dilactones by distillation or fractional dissolution,[4] to pass it directly through an alumina column, whereby the elution order is: monolactone, dilactone, trilactone, etc. Polymers, that are sometimes difficult to remove by recrystallization are retained very strongly on the column.

With the 14-membered dilactone ($n = 5$) Stoll and Rouvé reported a yield of less than 1%, and the higher concentration used here increased it only to 3%. An attempt was therefore made to prepare this compound by pyrolytic depolymerization of the corresponding polymer according to the method of Spanagel and Carothers.[6] The mixture of liquid mono- and solid di-lactones that distilled was separated and the monolactone returned to the still; repetition of this process three times, gave a 14% yield of dilactone. This procedure failed in attempts to prepare lower members; for $n = 4$, it is well known that the conversion of 6-membered monolactone into polyester is easy and reversible,[7] but oligolactones are not observed. Also, many other attempts to synthesize the 10- and 12-membered dilactones all failed, giving the 5- and 6-membered monolactones instead.

For the preparation of the cyclic diesters (II), depolymerization [6] was the obvious choice, since the desired diester is the most volatile of the possible products in equilibrium. By using hydrous stannous chloride as a catalyst in this remarkably simple and efficient method, all the diesters (II) from $n = 3$ to $n = 10$ were obtained in yields ranging from 6 to 60% (Table 2). It is of special interest that even the typical medium-sized 10-membered trimethylene glutarate ($n = 3$) was formed in 17% yield, and that the 14- and 18-membered rings represent yield maxima, as was also the case in the depolymerization of polyamides.[1] All these compounds are new, in spite of the fact that Carothers and his co-workers [6,8] prepared numbers of analogous diesters, which, however, all happen to be unsymmetrical.

TABLE 2.

Yields, analyses, and physical properties of cyclic diesters (II).

| | | | | | | | | Found | | | | Required | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $n$ | Yield (%) | M. p. | Crystal habit | $P_\infty$ (cm.$^3$) | $P_E$ (cm.$^3$) | $\mu$ (D) (±0·05D) | $\mu_{10\%}$ (D) | C (%) | H (%) | $M$ * | Formula | C (%) | H (%) | $M$ |
| 3 | 17 | 85° † | Plates or prisms | 165·0 | 39·2 | 2·48 | 2·44 | 55·9 | 7·0 | 171 | $C_8H_{12}O_4$ | 55·8 | 7·0 | 172 |
| 4 | 17 | 93 † | Needles or prisms | 87·7 | 48·2 | 1·43 | 1·34 | 60·15 | 8·1 | 196 | $C_{10}H_{16}O_4$ | 60·0 | 8·1 | 200 |
| 5 | 26 | 59 | Thin plates | 231·5 | 58·3 | 2·91 | 2·86 | 63·4 | 9·0 | 225 | $C_{12}H_{20}O_4$ | 63·1 | 8·8 | 228 |
| 6 | 16 | 64 | Needles or prisms | 144·3 | 66·8 | 1·95 | 1·86 | 65·5 | 9·7 | 252 | $C_{14}H_{24}O_4$ | 65·6 | 9·4 | 256 |
| 7 | 58 | 62 | Thin plates | 232·6 | 76·0 | 2·77 | 2·70 | 67·55 | 10·1 | 280 | $C_{16}H_{28}O_4$ | 67·6 | 9·9 | 284 |
| 8 | 32 | 68 | Prisms | 189·0 | 85·6 | 2·25 | 2·15 | 69·4 | 10·5 | 307 | $C_{18}H_{32}O_4$ | 69·2 | 10·3 | 312 |
| 9 | 6 | 73 | Plates | 239·6 | 94·3 | 2·67 | 2·58 | 70·7 | 10·9 | 330 | $C_{20}H_{36}O_4$ | 70·5 | 10·7 | 341 |
| 10 | 7 | 80 | Prisms | 226·2 | 105·1 | 2·43 | 2·33 | 71·65 | 11·1 | 359 | $C_{22}H_{40}O_4$ | 71·7 | 10·9 | 369 |

* By vapour-pressure osmometry in chloroform. † Starts subliming at 80°.

The physical properties are given in Tables 1 and 2, and in Figs. 3 and 4. The strong melting-point alternation of the dilactones (Fig. 3) is accompanied by an alternation in crystal form (Table 1), the higher-melting compounds crystallizing from hexane or benzene as needles, the lower-melting as thin plates. On the other hand, the melting points of the

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[6] Spanagel and Carothers, *J. Amer. Chem. Soc.*, 1935, **57**, 929; 1936, **58**, 654.

[7] Carothers, Dorough, and van Natta, *J. Amer. Chem. Soc.*, 1932, **54**, 761.

[8] Hill and Carothers, *J. Amer. Chem. Soc.*, 1933, **55**, 5031.

lower cyclic diesters (Fig. 3) show a slight opposite alternation, which disappears completely in the higher members of the series; this undecided behaviour is also observed in the crystal form (Table 2), which alternates slightly and not very clearly, in the opposite sense to that of the dilactones. An inversion of the melting point alternation might have been explicable as a pure dipole orientation effect, if it had disappeared quickly and changed over to the normal alternation of the dilactone series with increasing ring size. Thus, even the much stronger amide dipoles of the cyclic diamides[1] only attenuate, and do not invert, the normal melting point alternation, and the effect disappears rapidly with increase of ring size. It may be that secondary effects in the amides, such as the possibility of doubly associated chains being formed only when *n* is odd,[1] tend to preserve the alternation. It may also be that the lack of association in the cyclic diesters and dilactones permits other factors, such as molecular symmetry determining the orientational entropy change at the melting point, to play a relatively greater role. The dilactones in which *n* is odd, which are the only ones that can have centrosymmetric conformations (Fig. 1a), have therefore especially high melting points. The possibility was also considered that, as in the series of cycloalkanes, cycloalkanones, etc.,[2] the melting points represent only part of the melting process, and that the genuine alternation might be found in a solid-phase transition point. Against this are the following arguments: (*a*) " Melting points " of " rotating " ring compounds[2] vary less regularly, lie somewhat higher, and reach a maximum at about 18 or 19 ring atoms. (*b*) The diester crystals are not at all soft and " plastic," but hard and brittle. (*c*) The infrared spectra are different for the solid and for the melt; hence, selection of conformation does take place. (*d*) No transition point was found in the solid when it was examined in a differential thermal analyser.

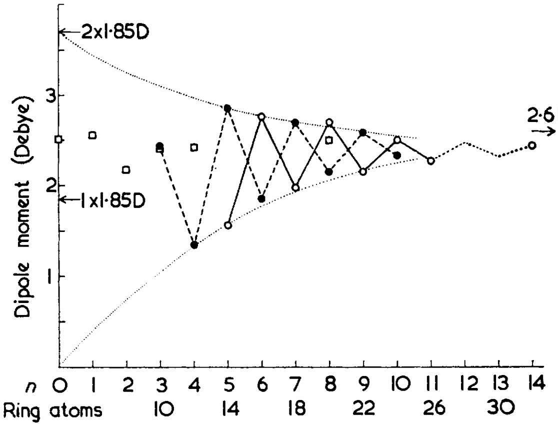

Fig. 4. Dipole moments of (○) dilactones (I), of (●) symmetrical cyclic diesters (II), and of (□) open-chain diesters $EtO_2C\cdot[CH_2]_n\cdot CO_2Et$.[9]

Observed dipole moments in benzene solution are given in Tables 1 and 2. The values obtained on the assumption that the atomic polarization is about 10% of the electronic polarization (molar refraction) are plotted in Fig. 4. The alternation, opposite in the two series, is exactly in the sense expected from the postulated conformations of Figs. 1 and 2. If these conformations were absolutely rigid, a stronger alternation would have been observed, the lower values approaching zero, and the higher values approaching twice the ester moment (2 × 1·85D). The fact that the two series (excluding the 10-membered diester) can be extrapolated to these values respectively when $n = 0$, suggests that the rapid damping of the alternation with ring size is due to thermal vibrations in the increasingly flexible ring, or to the presence of an increasing number of other, less stable, conformations in solution. The latter view is supported by the great differences between the infrared spectra of the solids and of their solutions (see below). At lower temperatures, the dipole moment alternation should therefore become stronger. It is interesting to note that both series seem to converge asymptotically to a value of about 2·4D with increasing ring size, as compared with the value $1\cdot85 \times \sqrt{2} = 2\cdot6$D calculated [9] for completely free orientation of the two ester groups. Reported dipole moments for diethyl esters of aliphatic dicarboxylic acids [9] have also been plotted in Fig. 4 and are already close to these limiting values in very short chains. The monotonic behaviour of this aliphatic series compared with the alternation of the cyclic compounds is a clear demonstration of the difference between open chains and rings; the number of strain-free conformations of open chains is almost limitless, compared with the restricted conformational possibilities in cyclic compounds.[2]

The somewhat low dipole moment of the 10-membered diester (II; $n = 3$) is anomalous. It is unlikely that it is due to a *cis*-configuration of one or both ester groups, which, considering the large dipole moment of the *cis*-ester,[3] would demand a nearly antiparallel relative orientation. Huisgen and Ott [3] have shown, by comparing dipole moments, boiling points, hydrolysis rates, and polymerization tendencies of monolactones, that the 10-membered ring is the first that accommodates exclusively the more stable *trans*-configuration. Furthermore, the amide groups of the corresponding diamide [1] are in the *trans*-configuration. The reduced value of the dipole moment may rather be a consequence of a distortion of the ring because of transannular repulsion, or an inductive effect across the ring.

The infrared spectra * of the dilactones and diesters are so rich in bands that no precise conclusions can be drawn from variations of those few bands whose assignments are certain. For this work, the main value of infrared spectra derives froma comparison of the spectra of the solids with those of solutions. The 10- and 12-membered cyclic diesters (II; $n = 3$ and 4) show the strongest spectral resemblance in the two states, indicating that these molecules are quite rigid and conformationally homogeneous even in solution. The 14-membered diester and, even more so, the dilactone ($n = 5$) have also rather similar spectra in the two states; since the solution spectra show well resolved bands, the number of new conformations must be very small. With further increase in ring size, the two series develop in a parallel manner. The 16-membered rings ($n = 6$), the spectra of whose solutions still retain some individuality, represent a transition to the larger rings, in the spectra of which more and more bands coalesce to broad unspecific absorption regions. This occurs especially between 1000 and 1250 cm.$^{-1}$, where the C–O and C–C single bonds in and near the ester group absorb strongly.[10] However, the typical spectrum of an open-chain aliphatic ester [3,10] is approached quite slowly, a ring size of 24 ring atoms ($n = 10$) being needed before its characteristic frequency and intensity pattern is reached (1240s, 1170vs, 1100m, and 1060m cm.$^{-1}$). As there is no reason to believe that the ester group changes its stable planar *trans*-configuration [3] in solution (the C=O band at 1730 cm.$^{-1}$ is very constant in position and intensity), it seems therefore that much of the conformational change takes place next to the ester groups. This may occur especially easily as the rotational energy barrier in the adjacent single bond should be very much reduced both on the " ether " side (in methyl formate [11a] the barrier is 1·2 instead of the normal 2·8 kcal./mole), and on the carbonyl side (in acetone [11b] the barrier is 0·8 kcal./mole). It is clear, however, that in ring systems such a change must necessarily be accompanied by a conformational change also within the polymethylene chains and, in fact, spectral changes do occur both in the methylene scissoring and rocking region (~1400 and ~700 cm.$^{-1}$) in the transition from the solid to the solution. It is noteworthy that a very sharp band at 1470 cm.$^{-1}$ (a frequency so high that a methylene vicinal to a C=O is excluded [12] and a relative intensity in the higher members so persistent that a methylene group vicinal to oxygen is also unlikely) and a sharp band at 715 cm.$^{-1}$ (a particularly low frequency for the in-phase rocking) are present in the solid-state spectra of the larger rings

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* These spectra will appear on punched cards in the DMS index.

[9] Smyth, " Dielectric Behavior and Structure," McGraw-Hill, New York, 1955, p. 371.

[10] Thompson and Torkington, *J.*, 1945, 640.

[11] (*a*) Curl, *J. Chem. Phys.*, 1959, **30**, 1529; (*b*) Swalen and Costain, *ibid.*, 1959, **31**, 1562.

[12] Jones and Sandorfy, in " Chemical Applications of Spectroscopy," Vol. IX of Weissberger, " Techniques of Organic Chemistry," Interscience, New York, 1956, p. 505.

only when $n$ is even; the spectra of solutions are similar for odd and even $n$ (highest scissoring at 1460 cm.$^{-1}$, broad rocking at 720 cm.$^{-1}$). As it is known, for example, that the methylene scissoring vibration of medium-sized cycloalkanes, etc., has a particularly high frequency when the ring tension is strong,[13] it is tentatively suggested that these sharp bands reflect the tension set up by the torsion of the polymethylene chain in the compact conformations of the type shown in Fig. 2a and b. This tension may be relieved by adoption of other (open) conformations when the molecule becomes solvated, with solvent molecules partially entering the " hole."

## EXPERIMENTAL

*Preparation of ω-Hydroxyalkanoic Acids.*—The half-ester of a dicarboxylic acid [14] ($C_5$—$C_{10}$) was refluxed with thionyl chloride [15] until no more hydrogen chloride was evolved (1—2 hr.). The excess of thionyl chloride was distilled off, and the ω-ethoxycarbonylalkanoyl chloride distilled at reduced pressure (~15 mm.) and reduced directly with sodium borohydride [16] in dioxan. Water was then added, and the acidified solution was extracted with ether to yield the crude ethyl ω-hydroxyalkanoate. This was hydrolysed by refluxing 10% sodium hydroxide solution for 1—2 hr. after which neutral substances were removed by extraction with ether. Acidification and extraction with ether yielded the free ω-hydroxyalkanoic acid, which was not further purified but was used for the cyclization after the neutralization equivalent had been checked by titration. The overall yields of crude $HO\cdot[CH_2]_n\cdot CO_2H$ were: 73 ($n = 4$), 73 ($n = 5$), 55 ($n = 6$), 50 ($n = 7$), 71 ($n = 8$), and 76 ($n = 9$).

*Dilactones* (I).—The members with $n = 10$, 11, 14, and 15, were kindly supplied by Dr. Max Stoll, Firmenich & Cie., Geneva. They were purified by chromatography on alumina (Woelm, activity 2), to remove a polymer that sometimes co-crystallized, and then by recrystallization from benzene or benzene–hexane. For the preparation of the members with $n = 5$—9, the high-dilution condensation method of Stoll and Rouvé [4] was modified. Since only dilactones and not monolactones were desired, more concentrated solutions were used: ~5 g. of ω-hydroxyalkanoic acid and ~3 g. of toluene-p-sulphonic acid were refluxed with 2·5 l. of benzene for 20 hr.; the yields were, however, very much reduced (Table 1). The products were isolated as follows: The cooled benzene solution was washed with aqueous sodium carbonate, dried, and distilled. The liquid residue was then chromatographed on alumina (Woelm, activity 1). The monolactone was eluted with hexane, the dilactone and, more slowly, the trilactone with benzene or ether–benzene. The dilactone was crystallized from hexane; the properties of these dilactones are given in Table 1.

The 14-membered dilactone ($n = 5$) was also prepared by polycondensation and subsequent depolymerization.[6] 6-Hydroxyhexanoic acid (4·0 g.) was dehydrated at 200° for 2 hr. in a small distillation flask fitted with a condenser. Stannous chloride dihydrate (0·08 g.) was then added to the resulting polymer and the temperature raised at reduced pressure (0·4 mm.). A mixture of liquid monolactone and crystalline dilactone distilled during 3 hr. The liquid was separated from the solid, returned to the distilling flask, equilibrated, and pyrolysed again. After three repetitions of this procedure, a total of 430 mg. of solid dilactone was obtained. Extraction of the distillation residue with benzene gave another 50 mg., so that the final yield was 14%, m. p. 116° after recrystallization from hexane. As much as 2·3 g. of monolactone (67%) was recovered.

Attempts to prepare the 12-membered dilactone ($n = 4$) by depolymerization failed. Only the monolactone distilled; it polymerized to a solid,[7] m. p. 45°, soluble in benzene, insoluble in hexane and ether. When the polymer was heated with magnesium chloride in an autoclave at 270° for 3 hr., no dilactone could be isolated from the equilibrium mixture.

Similarly, numerous attempts to prepare the 10-membered dilactone ($n = 3$) failed; the 5-membered γ-butyrolactone was always formed exclusively. Even heating of the monolactone with magnesium chloride in an autoclave at 300° gave no trace of polymer or dilactone; except for some carbonization, the monolactone was unchanged.

*Symmetrical Cyclic Diesters* (II).—Equimolar quantities of a dicarboxylic acid and an alkane-αω-diol (with 2 carbon atoms less) were heated for 3 hr. at 190° and atmospheric pressure.

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[13] Chiurdoglu, Doehard, and Tursch, *Bull. Soc. chim. France*, 1960, 1322.

[14] *Org. Synth.*, Coll. Vol. II, 1943, p. 276.

[15] Schmidt and Shirley, *J. Amer. Chem. Soc.*, 1949, **71**, 3804.

[16] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.

The pressure was then reduced to 2 mm. and heating continued for 4 hr. at 240°, giving a black viscous mass. Stannous chloride dihydrate (2% of the polymer weight) was then added, and the mixture heated to 325°/1 mm. The almost colourless distillate solidified at once. A benzene solution of this solid was passed through alumina (Woelm, activity 2), and the column washed with more benzene. The eluted solid was recrystallized from hexane (benzene–hexane for $n = 3$ and 4). Physical properties and analytical results are given in Table 2.

*Dipole-moment Determinations.*—For each compound, measurements were made at 25° of four solutions in benzene at different concentrations (mole fractions of solute ranging from about 0·003 to 0·014) following the procedure described by Weiss.[17] Dielectric constants were measured in a Slevogt Dipolmeter DM 01,[17] the densities pyknometrically, and the refractive indices at the sodium *D*-line in an Eintauchrefraktometer (Carl Zeiss, Jena). Extrapolation to infinite dilution was made according to Hedestrand; [18] the values lie on a straight line, indicating no association. Tables 1 and 2 show the values for the total molar polarization of the solute ($P_\infty$), for the electronic polarization ($P_E$) or molar refraction, and for the calculated dipole moment, first neglecting atomic polarization ($\mu$), and then assuming it to be 10% of $P_E$ ($\mu_{10\%}$). The latter values are plotted in Fig. 4.

*Infrared Spectra.*—These were measured on a Perkin-Elmer double-beam instrument, model 21, fitted with a sodium chloride prism. Potassium bromide discs were used for the solid-state spectra (2—15 $\mu$), and solution spectra were measured in carbon tetrachloride (2—12 $\mu$) and carbon disulphide (8—15 $\mu$).

The author is grateful to Dr. Max Stoll, Geneva, for samples of some of the dilactones, to Mr. Willy Verhaegen, Ghent, and Mr. Raymond Coulon for assistance in the synthetic work, and to Mr. André Gérondal for the determination of the dipole moments.

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[*Received, March 11th*, 1964.]

[17] Weiss, *Z. anorg. Chem.*, 1956, **287**, 223.

[18] Hedestrand, *Z. phys. Chem.*, 1929, *B***2**, 428.