Intramolecular Rearrangements of 1-Ethoxypropenyl Esters of γ- and δ-Keto Acids[1]

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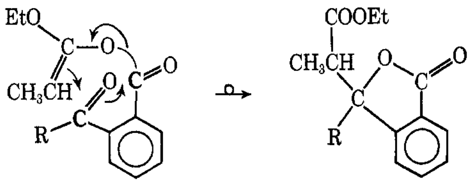
Pyrolysis of 1-ethoxypropenyl esters of phthalaldehydic, *o*-acetylbenzoic, and *o*-benzoylbenzoic acids afforded high yields of ethyl α-(1-phthalidyl)propionate (**7**), ethyl α-(1-methyl-1-phthalidyl)propionate (**8**), and ethyl α-(1-phenyl-1-phthalidyl)propionate (**9**), respectively. These compounds were also prepared by Reformatsky reactions of ethyl α-bromopropionate with ethyl phthalaldehydate, *o*-acetylbenzoate, and *o*-benzoylbenzoate, respectively. Thus, these pyrolytic reactions exemplify an alternate to the Reformatsky route. Pyrolysis of 1-ethoxypropenyl esters of 4-benzoyl-2,2-dimethylbutanoic and 4-benzoyl-3,3-dimethylbutanoic acids afforded high yields of 3,4-dihydro-3,3-dimethyl-6-phenyl-2-pyrone (**16**$_{\mathrm{UL}}$) and 3,4-dihydro-4,4-dimethyl-6-phenyl-2-pyrone (**17**$_{\mathrm{UL}}$), respectively, in addition to ethyl propionate. Pyrolysis of 1-ethoxypropenyl esters of 4-benzoylbutanoic and 4-benzoyl-4,4-dimethylbutanoic acids afforded 30 and 65% yields, respectively, of ethyl 3,7-diketo-2-methyl-7-phenylheptanoate (**20**) and ethyl 3,7-diketo-7-phenyl-2,6,6-trimethylheptanoate (**21**). The latter reactions represent a new method of synthesis for mono-α-substituted β-keto esters.

In earlier work[3] the thermal and boron fluoride catalyzed rearrangements of 1-ethyoxyvinyl esters of a variety of keto acids were described. The formation of the products could be explained by assuming that the reactions occur by bicyclic mechanisms.[3,4] The work herein described was undertaken to find out whether the reactions could be generalized by using 1-ethoxyalkenyl esters instead of 1-ethoxyvinyl esters. Since 1-ethoxypropyne is available,[5] 1-ethoxypropenyl esters were prepared from it and the same keto acids used previously[3] by reaction in methylene chloride containing mercuric acetate. The reactions of these acids with 1-ethoxypropyne were considerably slower than the corresponding reactions with ethoxyacetylene but afforded high yields of the desired esters.[6] In addition, 1-ethoxy-1-propenyl esters of phthalaldehydic (**1**), *o*-acetylbenzoic (**2**), *o*-benzoylbenzoic (**3**), and levulinic acid were prepared and studied.[6]

In order to obtain other substituted vinyl esters which might give analogous rearrangements, attempts were made to add *o*-benzoylbenzoic acid (**3**) to phenyl 1-propynyl sulfide,[7] phenyl 1-propynyl sulfone,[8] phenyl phenylethynyl ketone,[9] phenylacetylene, and 1-diethylamino-1-propyne,[10] using conventional mercuric salt catalysis. No reactions took place with the first four compounds, and the *n*,ψ-anhydride of *o*-benzoylbenzoic acid[11] was formed in 30% yield with 1-diethylamino-1-propyne.

On pyrolysis of 1-ethoxy-1-propenyl phthalaldehydate (**4**), 1-ethoxy-1-propenyl *o*-acetylbenzoate (**5**), and 1-ethoxy-1-propenyl *o*-benzoylbenzoate (**6**), rearrangement, presumably *via* the [3.2.1] bicyclic mechanism shown in Scheme I, led in high yields to the formation of the substituted phthalides **7**, **8**, and **9**, respectively.

SCHEME I



4, R = H
5, R = CH$_3$
6, R = C$_6$H$_5$

7, R = H
8, R = CH$_3$
9, R = C$_6$H$_5$

The structures of **7**, **8**, and **9** were supported by analytical, infrared, and nmr data. In each case hydrolysis to the corresponding acid was effected. The esters proved identical with the products obtained by reacting ethyl α-bromopropionate and zinc with normal ethyl phthalaldehydate, *o*-acetylbenzoate, and *o*-benzoylbenzoate, respectively. In our work we were unable to separate the mixture of diastereomeric lactone esters formed in the rearrangement reactions, but nmr spectra indicated that a mixture of isomers was at hand. The lactone esters formed by the Reformatsky reactions were likewise mixtures of stereoisomers.

In order to study similar rearrangements in the aliphatic series, 4-benzoylbutanoic acid (**10**), 4-benzoyl-2,2-dimethylbutanoic acid (**11**), 4-benzoyl-3,3-dimethylbutanoic acid (**12**), 4-benzoyl-4,4-dimethylbutanoic acid (**13**), and levulinic acid (**14**) were converted into their corresponding 1-ethoxy-1-propenyl esters, **15**, **16**, **17**, **18**, and **19**, as in the cases of acids **1**, **2**, and **3**. On pyrolysis at 180–200°, results similar to those obtained with the corresponding 1-ethoxyvinyl esters[3] were obtained. The main products in the cases of **15**, **16**, **17**, and **19** were ethyl propionate and the unsaturated lactones (UL) as shown in Scheme II.

As in previous cases in which unsaturated lactones were obtained on pyrolysis of 1-ethoxyvinyl esters,[3] we believe the reactions from **15**, **16**, and **17** to **15**$_{\mathrm{UL}}$, **16**$_{\mathrm{UL}}$, and **17**$_{\mathrm{UL}}$ proceed by a [4.2.2] bicyclic path as shown in Scheme III. The arguments are given[3] and need not be repeated. In the case of the reaction of **19** to **19**$_{\mathrm{UL}}$ a [4.2.1] bicyclic path is involved.

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[2] To whom correspondence should be addressed. Dr. Z. ud Din held an Ohio State University Postdoctoral Fellowship during 1968–1969.

[3] M. S. Newman and S. Gupte, *J. Org. Chem.*, **35**, 4176 (1970).

[4] M. S. Newman and C. Courduvelis, *J. Amer. Chem. Soc.*, **88**, 781 (1966).

[5] D. G. Farnum, M. A. T. Heybey, and B. Webster, *ibid.*, **86**, 673 (1964).

[6] Because of the complexity of the nmr spectra of these esters, we could not determine the ratio of the stereoisomers in all of the 1-ethoxy-1-propenyl esters involved.

[7] G. Pourcelot and P. Cadiot, *Bull. Soc. Chim. Fr.*, **9**, 3016 (1966).

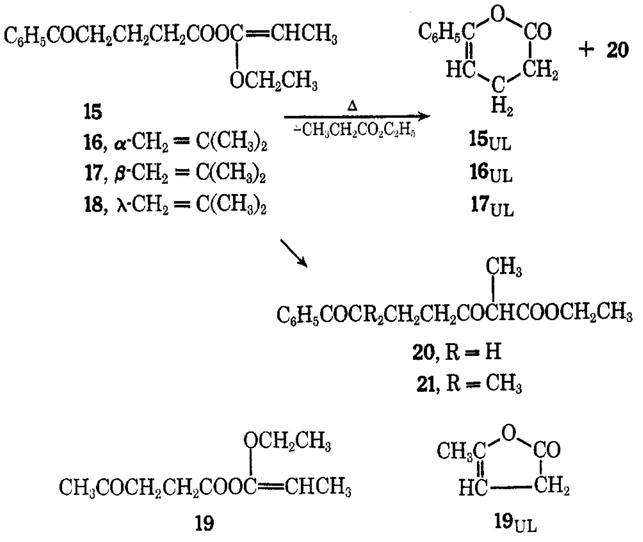
[8] W. E. Parham and P. L. Stright, *J. Amer. Chem. Soc.*, **78**, 4783 (1956).

[9] J. V. Nef, *Justus Liebigs Ann. Chem.*, 264, 308 (1899); M. S. Newman and B. C. Ream, *J. Org. Chem.*, **31**, 3861 (1966).

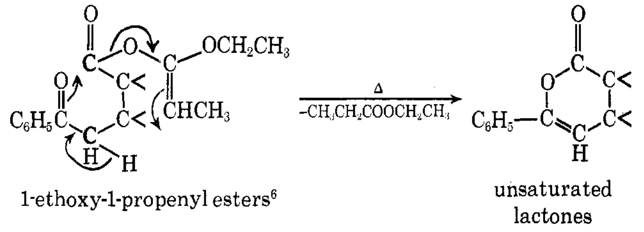
[10] J. Ficini and C. Barbara, *Bull. Soc. Chim. Fr.*, 871 (1964); 2787 (1965).

[11] M. S. Newman and C. Courduvelis, *J. Amer. Chem. Soc.*, **86**, 2942 (1964).

SCHEME II



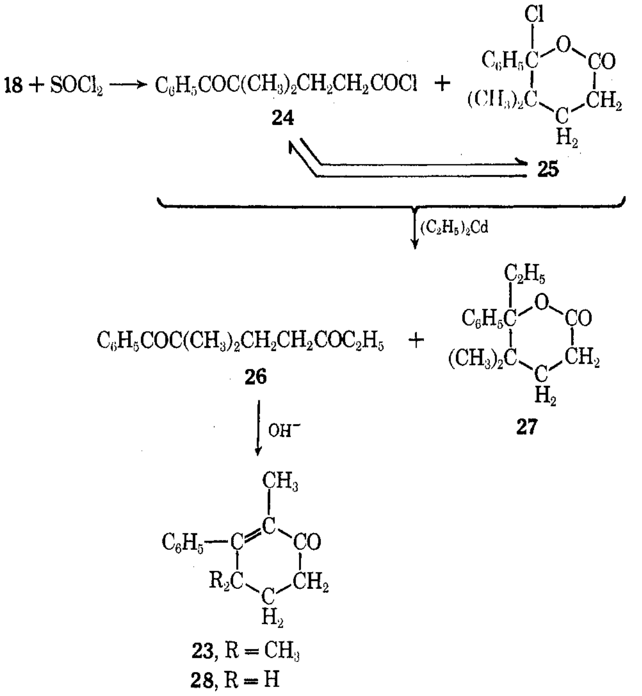
SCHEME III



On pyrolysis of **15**, a 30% yield of ethyl 3,7-diketo-2-methyl-7-phenylheptanoate (**20**) was obtained in addition to 60–64% of **15**$_{UL}$. Similarly, pyrolysis of **18** yielded 65% of ethyl 3,7-diketo-2,6,6-trimethyl-7-phenylheptanoate (**21**)[12] in addition to a 20% yield of the *n*,*n*-anhydride **22** of **13**. No unsaturated lactone is possible in the case of **18**. The formation of β-keto esters on pyrolysis of ethoxyvinyl esters has been reported in very low yield,[13] but this is the first example of pyrolysis of an alkylated ethoxyvinyl ester. Further work is needed to evaluate the value of this method for the preparation of monoalkylated unsymmetrical β-keto esters, as this route may prove an important one for this type of compound.

In attempts to hydrolyze **20** and **21** to the corresponding acids, heating with alkali or acid afforded small amounts of neutral products in addition to 40–50% yields of the acids **10** and **13**, respectively. The structure of the neutral product formed from **21** was established as 3-phenyl-2,4,4-trimethyl-2-cyclohexenone (**23**) by spectral data, analysis, and comparison with a sample synthesized as shown in Scheme IV. The formation of **23** from **21** is explained by assuming that hydrolysis of **21** yields the diketone **26** by decarboxylation of the diketo acid to be expected on hydrolysis of **21**. The diketone then undergoes an intramolecular aldol condensation followed by dehydration to **23**. Similar reactions lead to the formation of **28** from **15**.

SCHEME IV



The product resulting from the treatment of 4-benzoyl-4,4-dimethylbutanoic acid (**18**) with thionyl chloride was a mixture of the normal (**24**) and pseudo acid chlorides (**25**) as judged by the complexity of the carbonyl bands in the ir spectrum. The mixture of **24** and **25** was partly crystalline but no attempt was made to separate isomers. Treatment of this mixture with diethylcadmium produced a mixture of neutral compounds **26** and **27** in 93% yield. By heating with aqueous alcoholic sodium hydroxide this mixture reacted chemically and the products were separated into a neutral and an acidic component. The neutral component produced in small yield was **23**, formed undoubtedly by alkali-catalyzed cyclization of the **26** originally present. Acidification of the alkaline solution returned a hydroxy acid which rapidly cyclized to **27**. These results are of interest in connection with (a) the relative amounts of *n* and *ψ* acid chlorides formed on treatment of γ-keto acids with thionyl chloride and (b) the reactivity of *n* and *ψ* acid chlorides with organocadmium derivatives. Further study in these areas is contemplated.

In summary, 1-ethoxypropyne has been shown to react with a variety of γ- and δ-keto acids to give the corresponding 1-ethoxypropenyl esters in high yield. Pyrolysis of the 1-ethoxypropenyl esters of phthalaldehydic, *o*-acetylbenzoic, and *o*-benzoylbenzoic acids affords **7**, **8**, and **9** in good to excellent yields. The overall result is that the acids **1**, **2**, and **3** can be converted easily into **7**, **8**, and **9** by a route which is alternate to treatment of the normal methyl esters of **1**, **2**, and **3** with zinc and ethyl α-bromopropionate. If other alkylethoxyacetylenes were to be used in place of 1-ethoxypropyne the synthetic scheme illustrated in Scheme I would be general.

Experimental Section[14]

1-Ethoxypropyne.—This compound, bp 90.0–91.5°, was prepared in 63% yield as described[5] except that methyl bromide was

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(12) A study of the generality of this method of preparing monosubstituted β-keto esters is under way.

(13) B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas*, **82**, 593 (1963).

(14) All melting and boiling points are uncorrected but were taken with standardized thermometers. Analyses were by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer Infracord and nmr spectra on a Varian A-60 instrument. Identity of compounds with known compounds was established by comparison of spectra

used in place of methyl iodide. The 1-ethoxypropyne used was always purified by a further fractional distillation (with little loss) of material prepared as above.

1-Ethoxypropenyl Esters.—These esters were all prepared by the following general method. A solution of 3.78 g (0.045 mol) of 1-ethoxypropyne in 30 ml of dry methylene chloride was added during 15 min to a 100-ml round-bottomed flask containing 0.2 g of pure powdered mercuric acetate and cooled with a Dry Ice–acetone bath. A solution, or suspension, of 0.02 mol of the organic acid[15] in 30 ml of methylene chloride was added during 1.5 hr. The mixture was allowed to come to room temperature during 1–2 hr and was magnetically stirred for 24 hr. The methylene chloride solution was then rapidly washed with cold water and cold dilute potassium carbonate solution and was worked up as usual to yield the ethoxypropenyl esters as almost colorless, viscous oils that failed to yield crystals on attempts at low-temperature crystallization. These oils were not submitted for elemental analysis because they were unstable on attempted distillation or chromatographic purification. However, the ir and nmr spectra were consistent with the assigned structures. Evidence that stereoisomers were present was found by close examination of the spectra. The expected triplets for the methyl hydrogens in the ethoxy groups and the doublets for the methyl hydrogens of the methyl attached to the substituted vinyl groups were usually complex multiplets (coupling contants 7–8 Hz) in the δ 1.6–1.0 region.

Pyrolysis of 4, 5, and 6.—All pyrolyses were carried out in small tared round-bottomed flasks which had been carefully cleaned and steamed for 15–20 min before drying and use. After pyrolysis the flask was weighed. The loss in weight was assumed to be ethyl propionate, which was identified in one experiment by glpc. In the pyrolyses of **4**, **5**, and **6** no loss in weight occurred and the crude products **7**, **8**, and **9** were obtained in quantitative yield. Compound **9** consisted of a mixture of solid, mp 104–106°, and liquid isomers. The results are summarized in Table I.

TABLE I

PYROLYSES OF 1-ETHOXY-1-PROPENYL ESTERS

Starting ester	Temp, °C	Time, hr	Rearranged ester	Bp, °C	Yield, %[a]
4	170	1	**7**	125[b]	70
5	160	1	**8**	116[b]	83
6	200	1.5	**9**	104–106[c]	84[d]

[a] Yield of material isolated. [b] At 0.04 mm. [c] A liquid isomer was also present. [d] Yield by vacuum distillation or chromatography over alumina.

Pyrolysis of 1-Ethoxy-1-propenyl 4-Benzoylbutanoate (15).—After 5.7 g of **15** at 185 ± 5° was heated for 1 hr the reaction mixture was held at 80° in a rotary evaporator to constant weight. Assuming the loss was due to ethyl propionate (identified in a separate experiment by glpc), a 62% yield of ethyl propionate was obtained. Vacuum distillation of the remainder yielded 2.1 g (63%) of 3,4-dihydro-6-phenyl-2-pyrone ($\mathbf{15}_{\mathrm{UL}}$) as a colorless liquid which solidified. Recrystallization at low temperature from pentane–ether yielded a sample, mp 47.0–48.5°, which was identical with an authentic sample.[3] On exposure to water $\mathbf{15}_{\mathrm{UL}}$ rapidly yielded **10** quantitatively.

The residue remaining after distillation of $\mathbf{15}_{\mathrm{UL}}$ was washed with carbonate to remove any acid and $\mathbf{15}_{\mathrm{UL}}$. Chromatography on neutral alumina using benzene–ether afforded a liquid homogeneous fraction (by tlc) which on bulb-to-bulb distillation at 0.01 mm yielded 1.70 g (30%) of ethyl 3,7-diketo-2-methyl-7-phenylheptanoate (**20**): ir 5.73, 5.83 (shoulder), and 5.92 μ; nmr δ 0.65–3.77 [m, 13, $(C\mathbf{H}_2)_3$, $C\mathbf{H}C\mathbf{H}_3$, $OCH_2C\mathbf{H}_3$], 3.85–4.40 (m, 2, $OC\mathbf{H}_2CH_3$), 7.20–8.15 (m, 5, aromatic); uv max (ethanol) 242 mμ (ϵ 12,245).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.5; H, 7.2. Found: C, 69.2; H, 7.0.

In a typical experiment a solution of 1.1 g of **20** in 8 ml of 95% alcohol containing 1.1 g of sodium hydroxide and 1 ml of water was refluxed for 1.5 hr. From the acid fraction of the reaction products was isolated 0.37 g (48%) of **10** and from the neutral fraction 0.30 g (40%) of 2-methyl-3-phenyl-2-cyclohexenone (**28**), an almost colorless liquid: ir 5.95 μ; uv max (ethanol) 261 mμ (ϵ 12,440); nmr δ 1.47 (s, 3, $CH_3C{=}$), 1.40–2.55 [m, 6, $-(CH_2)_3-$], 6.72–7.41 (m, 5, aromatic).

Anal. Calcd for $C_{13}H_{14}O$: C, 83.9; H, 7.5. Found: C, 83.7; H, 7.7.

On hydrolysis of **20** in 20 ml of aqueous acetic acid containing 0.7 ml of sulfuric acid for 4 hr, similar amounts of **10** and **28** were obtained as in the case of alkaline hydrolysis.

Pyrolysis of 1-Ethoxy-1-propenyl 4-Benzoyl-2,2-dimethylbutanoate (16).—After 4.50 g of **16** at 200 ± 5° was heated for 1.5 hr the loss in weight was 1.25 g (83% calculated as ethyl propionate). The residue solidified on cooling. Crystallization from hexane–pentane yielded 2.80 g (94%) of 3,4-dihydro-3,3-dimethyl-6-phenyl-2-pyrone ($\mathbf{16}_{\mathrm{UL}}$), mp 71–72°, identical with authentic[3] **16** as shown by ir, nmr, and mixture melting point.

Pyrolysis of 1-Ethoxy-1-propenyl 4-Benzoyl-3,3-dimethylbutanoate (17).—After 5.0 g of **17** was heated at 200 ± 5° for 1.5 hr the loss in weight was 1.20 g (80% calculated as ethyl propionate). On bulb-to-bulb distillation near 120° at 0.4 mm there was obtained 2.80 g (85%) of 3,4-dihydro-4,4-dimethyl-6-phenyl-2-pyrone ($\mathbf{17}_{\mathrm{UL}}$). This liquid was shown to be identical with an authentic sample[3] by comparison of ir and nmr spectra.

Pyrolysis of 1-Ethoxy-1-propenyl 4-Benzoyl-4,4-dimethylbutanoate (18).—After 6.0 g of **18** was heated at 190 ± 5° for 1 hr the loss in weight was 0.63 g (31.5% calculated as ethyl propionate). An ether–benzene solution of the residue was extracted with dilute sodium carbonate, which yielded 0.6 g (14%) of **13** on acidification. Distillation then yielded 3.9 g (65%) of ethyl 3,7-diketo-γ-phenyl-2,6,6-trimethylheptanoate (**21**): bp 135–137° (0.3 mm); ir bands at 5.73, 5.83 (shoulder), and 6.04 μ; uv max (ethanol) 242 mμ (ϵ 15,490); mass spectrum, parent peak *m/e* 304 (calcd 304); nmr δ 0.68–1.58 [m, 13, $C(C\mathbf{H}_3)_2$, $-CHC\mathbf{H}_3$, $CCH_2C\mathbf{H}_3$], 1.85–2.65 (m, 4, $-(CH_2)_2-$], 3.90–4.38 (m, 2, $OC\mathbf{H}_2CH_3$), 7.18–7.82 (m, 5, aromatic).

Anal. Calcd for $C_{18}H_{24}O_4$: C, 70.9; H, 7.9. Found: C, 71.1; H, 7.8.

The residue from distillation of **21** proved to be the *n,n*-anhydride of **13**[3] (20% yield). Identity was established by ir and quantitative hydrolysis to **13**.

In a typical alkaline hydrolysis as for **20**, 1.0 g of **21** yielded 0.3 g of **18** and 0.5 g of a neutral fraction. On chromatography over neutral alumina 0.45 g (64%) of 3-phenyl-2,4,4-trimethyl-2-cyclohexenone (**23**) was obtained: mp 44.0–44.5°; ir 5.95 μ; nmr δ 1.10 [s, 6, $(CH_3)_2C$], 1.37 (s, 3, $CH_3C{=}$), 1.75–2.18 (m, 2, $(CH_3)_2CC\mathbf{H}_2$], 2.35–2.75 (m, 2, CH_2CO), 6.90–7.55 (m, 5, aromatic).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.1; H, 8.4. Found: C, 84.0; H, 8.5.

The same ketone (**23**) was obtained from an acid-catalyzed hydrolysis. These ketones were identical with a sample prepared as follows. To a solution of 8.0 g of **13** in 25 ml of methylene chloride was added 10 g of pure thionyl chloride. After the mixture was stirred at room temperature for 4 hr the volatile material was removed on a rotary evaporator. The resulting acid chloride was judged to consist mainly of the cyclic form **25** because of slight shoulders at 5.5 and 5.8 μ (which would be expected from the acyclic form **24**) on the main band at 5.63–5.70 μ in the infrared (Nujol mull). The Grignard reagent prepared from 1.5 g of magnesium and 6.7 g of ethyl bromide in 60 ml of ether was treated with 6.0 g of cadmium chloride.[16] This reagent was concentrated to 40 ml by distillation, and 40 ml of benzene was added. By distillation, 40 ml of solvent was removed, 40 ml of benzene was added to the residue, and solvent was distilled almost to dryness. The resulting solid was stirred with 40 ml of benzene and treated with a solution of the crude acid chloride in 40 ml of benzene. After being held at reflux for 1 hr, the mixture was treated with dilute H_2SO_4 and worked up as usual. From the alkaline wash was isolated 0.3 g of **13**. The neutral fraction weighed 7.5 g (93% calculated as **26** or **27**) and partly crystallized on trituration with petroleum ether (bp 30–60°) at low temperatures. A solution of 2.0 g of this neutral material was subject to alkaline hydrolysis for 2 hr. From the neutral fraction was isolated 0.15 g of **23**, identical with that described above (by ir

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and mixture melting point determinations when applicable. The phrase "worked up as usual" means that an ether–benzene solution of the products was washed with cold dilute alkali and/or acid and then with saturated salt solution, followed by filtration through a cone of anhydrous magnesium sulfate. All work was carried out in as nearly quantitative manner as possible. The solvent was then removed on a rotary evaporator under reduced pressure to constant weight. All experiments were repeated at least once for checking. All compounds had ir (Nujol, KBr pellets) and nmr (δ, CCl_4, TMS standard) spectra consistent with the assigned structures.

(15) All of the acids were obtained or prepared as described.[3]

(16) *Cf.* J. Cason and F. S. Prout, *J. Amer. Chem. Soc.*, **66**, 46 (1944).

and nmr). On acidification of the alkaline extracts containing the acidic portion of the hydrolysis products, lactonization occurred to yield 1.80 g of the lactone of 4,4-dimethyl-5-phenyl-5-hydroxyheptanoic acid as a colorless oil: bp 125° (0.05 mm); ir 5.74 μ; nmr δ 0.50–0.96 (m, 6, $>C(CH_3)(\mathbf{CH}_3)$, $CH_2\mathbf{CH}_3$), 1.09 (s, 3, $>C(\mathbf{CH}_3)(CH_3)$), 1.20–2.79 (m, 6-CH_2CH_2–, –$\mathbf{CH}_2$-CH_3), 7.30 (s, 5, aromatic).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.6; H, 8.6. Found: C, 77.6; H, 8.6.

Pyrolysis of 1-Ethoxypropynyl Levulinate (**19**).—After 3.6 g of **19** was heated at 200° for 1 hr, 1.7 g (94%) of ethyl propionate was collected. The nonacidic residue was essentially lactone $\mathbf{19}_{\mathrm{UL}}$, since 1.9 g (90%) of levulinic acid was obtained on treatment with aqueous sodium carbonate.

Ethyl α-(1-Phthalidyl)propionate (**7**).—A mixture of 15.0 g of phthalaldehydic acid, 17.2 g of ethyl iodide, 40 g of anhydrous potassium carbonate, and 400 ml of 2-butanone was held at reflux for 8 hr. Distillation of the neutral portion yielded 14.2 g (80%) of ethyl phthalaldehydate: bp 92–94° (5–6 mm);[17] ir 5.75 (CHO) and 5.81 μ ($COOC_2H_5$); nmr δ 10.61 (s, 1, CHO). The latter value establishes the aldehydo ester structure. A Reformatsky reaction involving 14.0 g of ethyl phthalaldehydate, 14.5 g of ethyl α-bromopropionate, 5.2 g of zinc, and 75 ml of 4:1 benzene–ether at reflux for 4 hr yielded 14.9 g (80%) of colorless **7**: bp 128–130° (0.1–0.2 mm); ir 5.63 and 5.76 μ; nmr δ 0.76–1.68 (m, 6, $CH\mathbf{CH}_3$, –$CH_2\mathbf{CH}_3$), 2.30–3.36 (m, 1, $>\mathbf{CH}CH_3$), 3.73–4.55 (m, 2, –$\mathbf{CH}_2CH_3$), 5.84 (d, $J = 4.5$ Hz, 1, –CH<), 7.30–8.15 (m, 4, aromatic).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.6; H, 6.0. Found: C, 66.5; H, 6.0.

This ester **7** proved identical with ester formed by pyrolysis of **4**, except for slight differences in content of the diastereomeric forms.

Ethyl α-(1-Methyl-1-phthalidyl)propionate (**8**).—Pure ethyl *o*-acetylbenzoate,[18] bp 100° (0.3–0.4 mm), ir 5.75 and 5.85 μ, nmr δ 2.40 (s, 3, CH_3CO), was obtained essentially as described for ethyl phthalaldehydate. By the Reformatsky route as described above for **7**, there was obtained 14.2 g of a crude product (from 17.1 g of ethyl *o*-acetylbenzoate) which showed (tlc) a small amount of product which moved faster than the main fraction. Chromatography on 350 g of neutral alumina (Woelm grade A) using petroleum ether yielded 11.5 g (52%) of **8**: bp 115–117° (0.2 mm); ir 5.62 and 5.77 μ; nmr δ 1.00–1.42 (m, 6, $>CH\mathbf{CH}_3$, –$CH_2\mathbf{CH}_3$), 1.75 (s, 3, CCH_3), 2.77–3.40 (m, 1, $>\mathbf{CH}CH_3$), 3.88–4.39 (m, 2, –$\mathbf{CH}_2CH_3$), 7.41–8.03 (m, 4, aromatic).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.7; H, 6.5. Found: C, 67.6; H, 6.4.

This ester **8** proved identical with ester formed by pyrolysis of **5**, except for slight differences in content of the diastereomeric forms.

Ethyl α-(1-Phenylphthalidyl)propionate (**9**).—A mixture of 5.08 g of ethyl *o*-benzoylbenzoate, 3.62 g of ethyl α-bromopropionate, 1.4 g of zinc, and 20 ml of 7:3 benzene–ether was held at reflux for 3 hr. After the usual work-up 6.4 g of crude neutral material was obtained. Chromatography over alumina (180 g) yielded 0.90 g (18%) of recovered ethyl *o*-benzoylbenzoate and 3.50 g (56%) of a mixture of solid and liquid isomers of **9**. The ir and nmr of the solid isomer were similar to that of the liquid which contained some of the solid isomer.

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.4; H, 5.8. Found (for solid isomer): C, 73.5; H, 5.9. Found (for liquid isomer): C, 73.6; H, 5.9.

Both the solid and liquid isomers of **9** were identical with similar fractions obtained by pyroysis of **6** except for slight differences in content of diastereomeric forms in the liquid fraction of **9**.

Registry No.—**4**, 30715-54-9; **5**, 30715-55-0; **6**, 30715-56-1; **7**, 30715-57-2; **8**, 30715-58-3; **9**, 30715-59-4; **15**, 30715-60-7; **15** (UL), 4055-00-9; **16**, 30708-61-3; **17**, 30788-19-3; **18**, 30788-20-6; **20**, 30788-21-7; **21**, 30788-22-8; **23**, 30708-62-4; **28**, 30708-63-5; 4,4-dimethyl-5-phenyl-5-hydroxyheptanoic acid lactone, 30708-64-6.

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[17] H. Meyer, *Monatsh. Chem.*, **25**, 497 (1904), reported bp 240–243°.

[18] S. Gabriel, *Ber.*, **29**, 2521 (1896), reported bp 279°.

Configuration and Conformation of the Long-Chain Cyclic Acetals of Glycerol[1]

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The structural and geometrical isomers of long-chain cyclic acetals of glycerol were prepared by acid-catalyzed condensation of glycerol with *n*-hexadecanal followed by purification of the individual components by adsorption and gas–liquid chromatography. The structures of the four isomers were established by chemical and spectroscopic means. Configurations and conformations were determined by 100-MHz nmr spectroscopy aided by deuterium labeling. The isomers were identified as *cis*-2-pentadecyl-5-hydroxy-1,3-dioxane (**1a**), *trans*-2-pentadecyl-5-hydroxy-1,3-dioxane (**2a**), *cis*-2-pentadecyl-4-hydroxymethyl-1,3-dioxolane (**3a**), and *trans*-2-pentadecyl-4-hydroxymethyl-1,3-dioxolane (**4a**). The lower energy structures are those having cis configuration. It was found that the six-ring isomers **1a** and **2a** differ in the orientation of their substituents at C-5, while the long-chain alkyl groups remain locked in equatorial conformation.

Long-chain cyclic acetals of glycerol have been found in lipid extracts from various organisms. However, much controversy still exists whether cyclic glycerol acetals are natural lipid constituents[2] or rather artifacts[3] produced during hydrolysis of plasmalogen-type lipids.[4] It is interesting to note that smooth muscle contracting activities, similar to those known for prostaglandins, have recently been ascribed to cyclic glycerol acetal phospholipids,[5] and it appears intriguing to speculate on the possible role of glycerol acetals in plasmalogen biosynthesis. Present knowledge of the chemical and physical properties of cyclic glycerol acetals in general is scarce.[6] Difficulties in the separation of the long-chain homologs and in the correlation of isomers are responsible for much of the confusion persisting in this field.

In this communication we report the preparation and characterization of the four structurally or geometrically isomeric, long-chain cyclic acetals of glycerol and of

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[2] W. Bergmann and R. A. Landowne, *J. Org. Chem.*, **23**, 1241 (1958); M. M. Rapport and N. F. Alonzo, *J. Biol. Chem.*, **235**, 1953 (1960); J. Ellingboe and M. L. Karnovsky, *ibid.*, **242**, 5693 (1967).

[3] M. F. Frosolono, A. Kisic, and M. M. Rapport, *J. Org. Chem.*, **32**, 3998 (1967).

[4] R. Pietruszko and G. M. Gray, *Biochim. Biophys. Acta*, **44**, 197 (1960); J. B. Davenport and R. M. C. Dawson, *Biochem. J.*, **79**, 10P (1961); J. B. Davenport and R. M. C. Dawson, *ibid.*, **84**, 490 (1962); R. Pietruszko and G. M. Gray, *Biochim. Biophys. Acta*, **56**, 232 (1962).

[5] R. A. Wiley, D. D. Sumner, and E. J. Walaszek, *Lipids*, **5**, 803 (1970).

[6] A. J. Showler and P. A. Darley, *Chem. Rev.*, **67**, 427 (1967); G. Aksnes, P. Albriktsen, and P. Juvvik, *Acta Chem. Scand.*, **19**, 920 (1965).