

acidification with sulfuric acid and extraction with four liters of benzene yielded 337 g. of a liquid acid mixture. On fractionation through a 25-plate column there were obtained fractions 1-10 inclusive, 150 g. of trimethylacetic acid m. p. and mixed m. p. of its anilide 130-131°, and fractions 11-20 inclusive, 109 g. of *t*-butylacetic acid, m. p. and mixed m. p. of its anilide 128-129°. The third component in the mixture was identified as dineopentylacetic acid, m. p. and mixed m. p. of its anilide 165-166°

Summary

1. The considerable resistance of 1,1-di-

neopentylethylene to oxidation has been confirmed.

2. 1,1-Dineopentylethylene can be readily obtained in about 15% yields from the oxidation of crude triisobutylene.

3. The oxidation of 1,1-dineopentylethylene by chromic acid mixture gives about 25% of dineopentylacetic acid and 50% of unchanged olefin.

STATE COLLEGE, PENNSYLVANIA RECEIVED JUNE 18, 1941

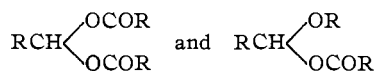
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Acylals

BY CHARLES D. HURD AND FRANK O. GREEN

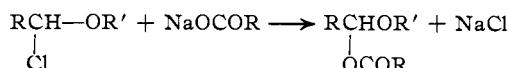
Ethers, acetals, esters and acid anhydrides all contain the C-O-C grouping. So also do such compounds as $\text{CH}_3\text{CH}(\text{OCOCH}_3)_2$ and $\text{C}_2\text{H}_5\text{OCH}_2\text{OCOCH}_3$, but these belong to none of the above four classifications. The general term "acylal" has been assigned¹ to compounds of this class. In general, an acylal function is a C-O-C grouping wherein one of the two carbons is in the aldehyde state of oxidation and the other is in the acid state of oxidation. For contrast, the C-O-C of acetals is an aldehyde-alcohol combination and that of esters an acid-alcohol combination.

The present study is devoted to the chemistry of acylals of these two general formulas



Strictly speaking the latter contains both acetal and acylal functions but it is convenient to refer to both types as acylals. There is no terminology for this class of substances as yet, but names comparable to those developed for acetals would assist in the visualization of these functional groups. Systematic names will be used in this paper.

1-Alkoxyalkyl chlorides were used in the synthesis of several mixed acetal-acylals in accordance with the equation



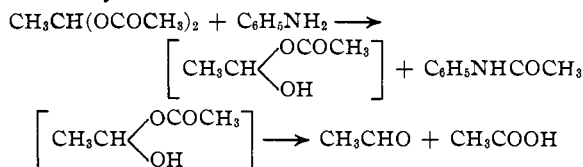
Except for 1-ethoxyethyl acetate, $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)\text{OCOCH}_3$, which Claisen² made by the reaction of acetic anhydride and ethyl acetal, no simple mixed acylals above the formaldehyde deriva-

tives have been reported. Several such mixed acylals, $\text{CH}_2(\text{OR})\text{OCOR}$, were prepared by Fife, Clark and Garland.³ Another substance of this type which has been reported is 2,2,2-trichloro-1-ethoxyethyl acetate,⁴ $\text{CCl}_3\text{CH}(\text{OC}_2\text{H}_5)\text{OCOCH}_3$. It was prepared by the reaction of acetyl chloride and chloral alcoholate. A list of the several acetal acylals formed in the present investigation together with their physical properties is submitted in Table I. Analytical results are included also. All combustions except that for 1-propoxyethyl propionate were carried out by Mr. Ernest Washburn.

Calculation of the molecular refractivities of the fourteen new compounds showed close agreement with the values obtained with the Lorenz-Lorentz formula, $M(n^2 - 1)/d(n^2 + 2)$.

Several new reactions of acylals were investigated. Ethylidene acetate was used throughout since it was the most readily available acylal. The reactions studied were those with aniline, hydroxylamine, and chlorine.

Acetanilide, acetic acid and acetaldehyde were the products of reaction with aniline. From the results it is apparent that only one of the two acetate radicals functions as an acetylating agent and the intermediate hemiacylal decomposes spontaneously.



(1) Hurd and Cantor, *THIS JOURNAL*, **60**, 2678 (1938).

(2) Claisen, *Ber.*, **31**, 1018 (1898).

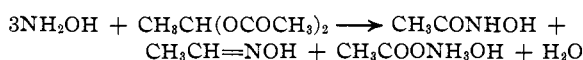
(3) Fife, Clark and Garland, *THIS JOURNAL*, **47**, 2421 (1925).

(4) Meyer and Dulk, *Ann.*, **171**, 69 (1874).

TABLE I
 PHYSICAL PROPERTIES AND ANALYSES

| Names | B. p. | | n_D^{20} | d_4^{20} | Formula | Analyses, % | | | |
|---------------------------|-----------|-----|------------|------------|--|-------------|-------|-------|-------|
| | °C. | mm. | | | | Calcd. | Found | | |
| 1-Methoxyethyl acetate | 24-25 | 15 | 1.3870 | 0.9736 | C ₅ H ₁₀ O ₃ | 50.84 | 8.53 | 50.80 | 8.45 |
| 1-Methoxyethyl propionate | 41-43 | 18 | 1.3936 | .9573 | C ₆ H ₁₂ O ₃ | 54.53 | 9.15 | 54.37 | 9.13 |
| 1-Methoxyethyl butyrate | 44-45 | 11 | 1.3989 | .9374 | C ₇ H ₁₄ O ₃ | 57.52 | 9.65 | 57.34 | 9.72 |
| 1-Ethoxyethyl propionate | 51.0-51.5 | 18 | 1.3967 | .9399 | C ₇ H ₁₄ O ₃ | 57.52 | 9.65 | 57.40 | 9.77 |
| 1-Ethoxyethyl butyrate | 55-56 | 11 | 1.4022 | .9211 | C ₈ H ₁₆ O ₃ | 59.94 | 10.06 | 59.81 | 10.11 |
| 1-Propoxyethyl acetate | 54-55 | 20 | 1.3977 | .9248 | C ₇ H ₁₄ O ₃ | 57.52 | 9.65 | 57.30 | 9.80 |
| 1-Propoxyethyl propionate | 54.8-55.2 | 11 | 1.4028 | .9194 | C ₈ H ₁₆ O ₃ | 59.94 | 10.06 | 59.80 | 10.31 |
| 1-Propoxyethyl butyrate | 67.8-69 | 11 | 1.4060 | .9131 | C ₉ H ₁₈ O ₃ | 62.04 | 10.41 | 61.95 | 10.40 |
| 1-Butoxyethyl acetate | 69.5-70 | 21 | 1.4031 | .9193 | C ₈ H ₁₆ O ₃ | 59.94 | 10.06 | 59.76 | 9.99 |
| 1-Butoxyethyl propionate | 70-71 | 11 | 1.4080 | .9108 | C ₉ H ₁₈ O ₃ | 62.04 | 10.41 | 61.95 | 10.50 |
| 1-Butoxyethyl butyrate | 80-81 | 11 | 1.4101 | .9013 | C ₁₀ H ₂₀ O ₃ | 63.79 | 10.71 | 63.67 | 10.60 |
| 1-Ethoxypropyl acetate | 46.3-46.8 | 14 | 1.3970 | .9299 | C ₇ H ₁₄ O ₃ | 57.52 | 9.65 | 57.62 | 9.65 |
| 1-Ethoxybutyl acetate | 53-54 | 10 | 1.4020 | .9202 | C ₈ H ₁₆ O ₃ | 59.94 | 10.06 | 59.78 | 10.06 |
| 1-Ethoxybutyl propionate | 66-67 | 10 | 1.4070 | .9133 | C ₉ H ₁₈ O ₃ | 62.04 | 10.41 | 61.84 | 10.54 |

The course of the reaction with hydroxylamine was analogous. Acetohydroxamic acid, acetaldoxime and hydroxylammonium acetate were characterized as reaction products



A procedure for identification of the reaction products had to be developed. Acetaldoxime was removed by vacuum distillation and the other two products were characterized by their difference in behavior on oxidation. When permanganate was added to acetohydroxamic acid a brown-colored solution was formed. Similar oxidation of hydroxylammonium acetate yielded a colorless solution. When permanganate was added to a mixture of hydroxylammonium acetate and acetohydroxamic acid, none of the brown color appeared until all the hydroxylammonium acetate had been oxidized. The reagent thus acted as its own indicator. An obscure end-point prevented quantitative accuracy, but it was shown in five titrations of hydroxylammonium acetate that 0.32-0.40 g. of potassium permanganate was consumed for each gram of hydroxylammonium acetate.

Chlorination of ethylidene acetate was negligible at room temperature, but the reaction was rapid at 100°. The most abundant reaction products were chloral, dichloroacetaldehyde, acetic acid, and chloroacetic acid. Some high-boiling product was formed also, which appeared to be a mixture of 2-chloroethylidene acetate, ClCH₂CH(OCOCH₃)₂, and 2,2-dichloroethylidene acetate, Cl₂CHCH(OCOCH₃)₂. Apparently chlorination was more rapid on the methyl group of the alde-

hyde function than on the methyl group of the acid function.

Experimental Part

Six 1-alkoxyalkyl chlorides were prepared according to the procedure of Shoemaker and Boord,⁵ by conducting dry hydrogen chloride into an aldehyde-alcohol mixture at 0 to 5°. Four of the substances were made from acetaldehyde, one from propionaldehyde, and one from *n*-butyraldehyde. These compounds were: 1-methoxyethyl chloride, 1-ethoxyethyl chloride, 1-propoxyethyl chloride, 1-butoxyethyl chloride, 1-ethoxypropyl chloride, and 1-ethoxybutyl chloride, yields averaged 80%. The chlorides were used without distillation, as recommended by Shoemaker and Boord.

Preparation of Acylals

Mixed alkyl acyl acylals were prepared by interaction of the above chlorides and various sodium salts. Details for one typical synthesis will be given.

Three-tenths mole (28.6 cc.) of 1-methoxyethyl chloride, CH₃CHClOCH₃, was chilled to 0° and added all at once to 0.4 mole (32.8 g.) of fused, pulverized sodium acetate. The mixture was shaken vigorously, whereupon heat was evolved. The shaking was continued for a few minutes while the evolution of heat lasted, then the flask was warmed over a low flame, with continued shaking, for five to ten minutes longer. The liquid was separated from the solid by vacuum filtration, with the aid of dry ethyl ether as an extraction solvent. The ether solvent was removed and the remaining oil distilled. The first fraction, collected below 29° (23 mm.), weighed 1.08 g. Then 18.84 g. was collected at 29-31° (23 mm.), leaving a liquid residue of 2.43 g. Redistillation of the main fraction showed the boiling point of 1-methoxyethyl acetate to be 24-25° at 15 mm. The 18.84 g. of crude product is a 51% yield based on the methoxyethyl chloride. The liquid residue was not further investigated. It was encountered in every preparation and boiled 40 to 50° higher. The results from this method are to be found in Table I. Yields were usually about 50% for the various acylals, but actual yields varied from 40 to 74%.

(5) Shoemaker and Boord, *THIS JOURNAL*, **53**, 1505 (1931).

Reaction with Aniline

A mixture of 15 g. of ethylidene acetate (b. p. 63–64° at 14 mm.), 10 cc. of dry ether and 10 cc. of aniline was left for one hour at room temperature. An odor of acetaldehyde developed during this period. To separate the acetaldehyde from the acetic acid and acetanilide which were present also, air was drawn through the mixture for an hour and the air stream was passed through potassium permanganate solution held at about 50°. Then the excess of permanganate was reduced by sodium bisulfite to manganese dioxide which was filtered off. The filtrate was concentrated, acidified with sulfuric acid, and distilled to obtain its acetic acid content. Neutralization of the distillate yielded 1.5 g. of sodium acetate. From this, *p*-bromophenacyl acetate (m. p. 84–85°) was prepared in the usual way.

The mixture from which the acetaldehyde was removed was distilled and the first fraction was chiefly acetic acid. Neutralization and evaporation yielded 5.2 g. of sodium acetate, identity of which was confirmed as the *p*-bromophenacyl ester. The higher-boiling part of the reaction products was chiefly acetanilide (b. p. 170–175° at 18 mm.). It melted at 112°; yield 7.8 g. From the products isolated, these yields were obtained: acetaldehyde, 0.8 g., 17.5%; acetic acid, 3.8 g., 61%; acetanilide, 7.8 g., 56.5%.

Reaction with Hydroxylamine

An analytical method for the identification of a mixture containing hydroxylamine, an oxime, and a hydroxamic acid was developed as follows. The mixture taken contained ethyl alcohol, acetaldoxime, acetoxyhydroxamic acid, and hydroxylammonium acetate. The first two liquids were distilled off under diminished pressure and the distillate redistilled for the oxime fraction at 110–115°. The hydroxylammonium ion was oxidized from the solid residue by addition of potassium permanganate solution (2 to 5% strength) till a permanent brown color remained. Between 0.32–0.40 g. of solid potassium permanganate was needed to oxidize 1 g. of hydroxylammonium acetate. The acetoxyhydroxamic acid which remained was converted to benzoylacetohydroxamic acid, m. p. 97–99°, which was filtered off. The acetate ion in the filtrate, indicative of hydroxylammonium acetate, was converted to sodium acetate which was characterized as *p*-bromophenacyl acetate, m. p. 83–84°.

From a synthetic mixture of acetaldoxime (4 g.), acetoxyhydroxamic acid (5.1 g.), and hydroxylammonium acetate (6.3 g.) and absolute alcohol (5 cc.) these quantities were identified: acetaldoxime as such, 50%; acetoxyhydroxamic acid as the benzoyl derivative, 20%; hydroxylammonium acetate as sodium acetate trihydrate, 24%. The details used were the same as those listed below. Yields from the reaction mixture obtained below should be interpreted in accordance with the yields obtained on the known mixture.

To a mixture of 15 g. of ethylidene acetate and 5 cc. of absolute alcohol at 0° was added 12.7 g. of pure hydroxylamine base.⁶ The temperature of the mixture rose to 30°. The mixture was distilled at 15 mm., whereupon 18 cc. of liquid was collected at 28–32°. Residue (R) will be referred to later. Redistillation of the 18 cc. yielded 1.6 cc. of alcohol at 76–89°, 2.8 cc. at 89–112°, 8.5 cc. at 115–120°.

(6) Hurd, "Inorganic Syntheses," McGraw-Hill Book Company, New York, N. Y., 1939, Vol. I, p. 87.

Both of the last two fractions contained acetaldoxime and acetic acid. From the 2.8-cc. fraction was isolated 0.56 g. of acetaldoxime, and from the 8.5-cc. fraction 1.32 g. This was done by adding wet ether to the fractions and then extracting the acetic acid into a water layer with dilute sodium carbonate solution. The ether layer was separated, dried over calcium chloride and distilled. Most of the oxime boiled at 114–115.5° and the yield was 31%.

Residue (R) required 8 cc. of 5% potassium permanganate solution to impart a green color. This was performed in an ice-bath. This color changed to brown when warmed to 25°. The solution was made basic with 18 cc. of 10% sodium hydroxide solution, then 5 cc. of benzoyl chloride was added. The mixture was shaken and cooled. There separated 4.6 g. of solid which was filtered off. The filtrate contained acetic acid. It was acidified, distilled, the distillate neutralized and evaporated to yield 3.6 g. (24%) of sodium acetate trihydrate. *p*-Bromophenacyl acetate, made from the latter, melted at 83–84°. The 4.6 g. of solid contained 0.76 g. of benzoic acid which was extracted with hot ligroin. The remaining 3.84 g. (21%) of benzoylacetohydroxamic acid was dissolved in ether. From it, crystals separated melting at 96–98°.

Reaction with Chlorine

A rapid stream of dry chlorine was bubbled through 15 g. of ethylidene acetate maintained at 90–100° for four hours. A reflux condenser was attached to the reaction flask. From the effluent gas only about 0.5 g. of a corrosive, fuming liquid was condensed by an efficient coil condenser maintained between –10 and –15° by ice and salt. The bulk of product, which remained in the reaction flask, weighed 20 g. Distillation yielded four fractions (°C., g.): 97–102, 4.7; 102–113, 4.7; 113–115, 4.1; 140–160, 1.5. The first fraction was viscous, fumed in air, and was soluble in water or ether. It reacted with 2,4-dinitrophenylhydrazine to produce a mixture of substances from which two products were isolated. One, which was glyoxal 2,4-dinitrophenylosazone,⁷ melted at 316–318° (uncor.). Other evidence for it was its orange color, its insolubility in alcohol, and its negative test for chlorine. The other substance isolated melted at 291–293°, and this was duplicated when an authentic specimen of chloral reacted with 2,4-dinitrophenylhydrazine. This evidence supports the contention that both dichloroacetaldehyde and chloral were in the first fraction.

The third fraction was composed chiefly of acetic acid. From it *p*-bromophenacyl acetate, m. p. 84°, was synthesized.

Ethylidene acetate was chlorinated at 100° as before and 5.3 g. of the chlorinated product was mixed with 6.5 cc. of *n*-butyl alcohol. This mixture was warmed on a steam-bath and left overnight, by which time two layers had formed. The lower layer (1.25 cc.) was a fuming liquid which yielded glyoxal 2,4-dinitrophenylhydrazone. Fractionation of the top layer was as follows (°C., cc.): 90–95, 1.25; 120–130, 4.0; 160–176, 0.6; 178–180, 1.8. The first fraction was a fuming liquid, evidently a chlorinated aldehyde. The other fractions possessed pleasant ester-like odors. Fraction 2 was chiefly butyl acetate. After redistillation (b. p. 120–122°) its saponification equivalent was

(7) Strain, THIS JOURNAL, 57, 760 (1935).

found to be 119 (calcd., 116). The fourth fraction was butyl chloroacetate. It was changed in 80% yield to chloroacetamide, m. p. 119–120°, and no trace of dichloroacetamide (m. p. 98–99°) could be found.

Summary

The C—O—C grouping in aldehyde-acid combinations is an acylal function. Fourteen new acylals were synthesized having the general formula: $\text{RCH} \begin{matrix} \text{OR} \\ \text{OCOR} \end{matrix}$, wherein R represents methyl, ethyl, propyl, or butyl radicals. These were prepared by reaction of a sodium salt with a 1-alkoxyalkyl chloride.

Ethylidene acetate was selected as a typical acylal for study with three new reactions, namely, with aniline, hydroxylamine, and chlorine. Reaction products with aniline were acetanilide, acetic acid, and acetaldehyde. Reaction products with hydroxylamine were acetohydroxamic acid, hydroxylammonium acetate, and acetaldoxime. Reaction products with chlorine were chloral, dichloroacetaldehyde, acetic acid, chloroacetic acid, 2-chloroethylidene acetate, and 2,2-dichloroethylidene acetate. The significance of these results is discussed briefly.

EVANSTON, ILLINOIS

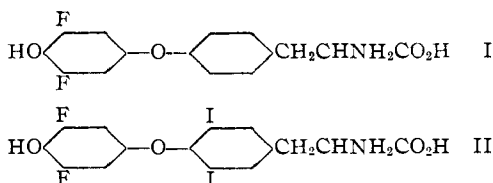
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[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 833]

The Synthesis of 3',5'-Difluoro-*dl*-thyronine and 3,5-Diiodo-3',5'-difluoro-*dl*-thyronine

BY CARL NIEMANN, ANDREW A. BENSON AND JAMES F. MEAD

Recent studies reported by Boyer, Evans and Phillips¹ have shown marked differences in the toxicity and physiological behavior of 3-fluoro- and 3,5-difluoro-*dl*-tyrosine.² In order to provide suitable compounds for an analogous study in the thyronine series, we previously synthesized 3'-fluoro-*dl*-thyronine and some of its iodinated derivatives.³ In continuation of this phase of our work we now wish to report the synthesis of 3',5'-difluoro-*dl*-thyronine (I) and 3,5-diiodo-3',5'-difluoro-*dl*-thyronine (II).⁴



The synthesis of these two compounds demanded as an intermediate 3,5-difluoro-4-methoxyphenol which was prepared in a 3.3% over-all yield by a series of reactions: anethole $\xrightarrow{74\%}$ 3-

nitro-4-methoxybenzoic acid $\xrightarrow{86\%}$ methyl 3-nitro-4-methoxybenzoate $\xrightarrow{91\%}$ methyl 3-amino-4-methoxybenzoate $\xrightarrow{49\%}$ methyl 3-fluoro-4-methoxybenzoate $\xrightarrow{72\%}$ methyl 3-fluoro-4-methoxy-5-nitrobenzoate $\xrightarrow{92\%}$ methyl 3-fluoro-4-methoxy-5-aminobenzoate $\xrightarrow{30\%}$ methyl 3,5-difluoro-4-methoxybenzoate $\xrightarrow{98\%}$ 3,5-difluoro-4-methoxybenzoic acid $\xrightarrow{91\%}$ 3,5-difluoro-4-methoxybenzamide $\xrightarrow{77\%}$ 3,5-difluoro-4-methoxyaniline $\xrightarrow{86\%}$ 3,5-difluoro-4-methoxyphenol. A second synthesis, giving an over-all yield of 9.0% was based on the following reactions: *o*-fluoroanisole $\xrightarrow{37\%}$ 2-fluoro-6-nitrophenol $\xrightarrow{86\%}$ 2-fluoro-6-nitroanisole $\xrightarrow{84\%}$ 2-fluoro-6-aminoanisole $\xrightarrow{48\%}$ 2,6-difluoroanisole $\xrightarrow{88\%}$ 2,6-difluoro-4-nitroanisole $\xrightarrow{93\%}$ 3,5-difluoro-4-methoxyaniline $\xrightarrow{86\%}$ 3,5-difluoro-4-methoxyphenol.

This phenol was condensed with triiodonitrobenzene and the resulting substituted diphenyl ether converted into 3,5-diiodo-3',5'-difluoro-*dl*-thyronine (II) by following the general method used by Harington and Barger⁵ for the synthesis of 3,5-diiodo-*dl*-thyronine. Partial dehalogenation of 3,5-diiodo-3',5'-difluoro-*dl*-thyronine (II) gave 3',5'-difluoro-*dl*-thyronine (I).

In the second synthesis of 3,5-difluoro-4-methoxyphenol

(5) C. R. Harington and G. Barger, *Biochem. J.*, **21**, 169 (1927).

(1) P. D. Boyer, R. J. Evans and P. H. Phillips, *Proceedings of the American Society of Biological Chemists*, 35th Annual meeting, Chicago, 1941, p. xx.

(2) J. English, Jr., J. F. Mead and C. Niemann, *THIS JOURNAL*, **62**, 350 (1940).

(3) C. Niemann, J. F. Mead and A. A. Benson, *ibid.*, **63**, 609 (1941).

(4) This research is being conducted as a cooperative project with Professor Paul Phillips of the University of Wisconsin who has undertaken a pharmacological investigation of the compounds reported in this and earlier communications.^{2,4}