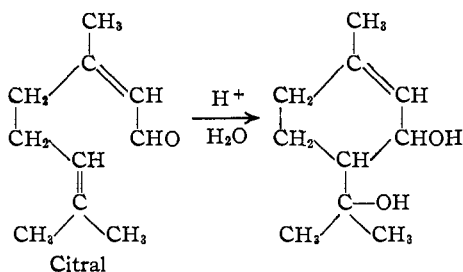


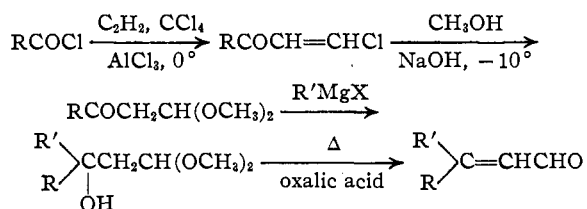
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

The Synthesis of Some α,β -Unsaturated Aldehydes¹BY CHARLES C. PRICE AND JOSEPH A. PAPPALARDO²

On the basis of an analysis of the kinetics of the process, together with pertinent knowledge from the literature on acid transformations, Price and Dickman³ proposed that the rapid disappearance of citral and citronellal in dilute aqueous solutions was due to a cyclic Prins-type reaction, involving condensation of the aldehyde carbonyl group with the remote double bond.



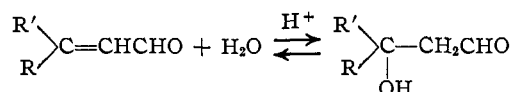
It seemed of some interest to test the proposed scheme by preparing that isomer of citronellal in which the double bond is conjugated to the carbonyl group, which we have termed "dihydrocitral" for convenience. Since catalytic as well as chemical reduction procedures, applied to citral, reduce the double bond conjugated to the carbonyl group preferentially, forming citronellal, we have explored the preparation of dihydrocitral, and a few homologs, according to the scheme outlined below.



The experimental results of the preparative scheme are summarized in Table I. Conversion from isoheptanoyl chloride to dihydrocitral was accomplished in about 20% over-all yield. It should be emphasized that methyl chlorovinyl ketone must be handled with care as it is strongly lachrymatory and vesicant. The chlorovinyl ketones of higher molecular weight did not show these characteristics.

Examination of the rates of disappearance of dihydrocitral in dilute aqueous hydrochloric acid (Table II) by disappearance of carbonyl group (by hydroxylamine sulfate) and of carbon-carbon double bond (by bromine titration) indicated far

greater stability than for citral or citronellal. Since the carbonyl group is stable, there is evidently opportunity for addition of water to the α,β -double bond, as indicated by drop in unsaturation. Winstein and Lucas⁴ have studied the similar equilibrium for crotonaldehyde-aldol in *ca.* *N* acid. Our data in 1.8×10^{-3} *N* acid indicate that equilibration for dihydrocitral proceeded much more rapidly and that the equilibrium for hydration is evidently somewhat less favorable, both reasonable expectations. These differences



are as to be expected since the hydration product of dihydrocitral is a tertiary rather than a secondary alcohol.

Experimental⁵

β -Chlorovinyl Ketones.—The general procedure of Carpmaels⁶ and of Yakubovich and Merkulova⁷ was followed. The acyl chloride (1.0 mole) was added to a well-stirred ice-cold suspension of aluminum chloride (1.1 moles) in *ca.* 300 ml. of carbon tetrachloride in a reaction system protected from moisture. Acetylene, dried by bubbling through sulfuric acid, was passed in a rapid stream through the stirred suspension maintained at 0–5°. Absorption of acetylene usually began within half-an-hour and addition was continued for half-an-hour after the rapid absorption ceased. The reaction mixture was then poured onto an ice and saturated salt solution, the aqueous layer extracted several times with ether, the combined washings dried and twice distilled.

Methyl β -chlorovinyl ketone must be handled with great care. It is intensely lachrymatory and caused severe blistering of the skin. It decomposes within a day or so at room temperature but solidifies at about 5° and is much more stable in solid form.

The higher homologs, such as isoamyl β -chlorovinyl ketone, decomposed only slowly and were non-vesicant and non-lachrymatory.

β -Ketoaldehyde Dimethyl Acetals.—The general procedure disclosed by Nelles⁸ was used. Over a two-hour period, a solution of sodium hydroxide (1.05 moles) in 350 ml. of absolute methanol was added to a stirred solution of β -chlorovinyl ketone (1.0 mole) in 150 ml. of absolute methanol, maintained at –15° to –10° in an ice-salt-bath. The reaction mixture was then poured into a liter of ice-cold saturated salt solution and extracted with four 100-ml. portions of ether. The combined extracts were dried and distilled with a pinch of potassium carbonate added.

For the ketobutyraldehyde dimethyl acetal, the product was isolated by filtration of the salt from the methanolic reaction mixture and then vacuum-fractional distillation of the filtrate. This product gave a deep red color with alcoholic ferric chloride (undoubtedly due to hydrolysis to

(4) Winstein and Lucas, *THIS JOURNAL*, **59**, 1461 (1937).(5) Elementary analyses by Micro-Tech Laboratories, Skokie, Ill. (6) Carpmaels, British Patent 461,080 (1936); (*C. A.*, **31**, 4676 (1937)).(7) Yakubovich and Merkulova, *J. Gen. Chem. (U. S. S. R.)* **16**, 55 (1946); (*C. A.*, **41**, 91 (1947)).(8) Nelles, British Patent 466,890 (1937) (*C. A.*, **31**, 7886 (1937)).

(1) Abstracted from the Ph.D. thesis submitted to the University of Notre Dame by Joseph A. Pappalardo.

(2) E. I. du Pont de Nemours and Co., Parlin, N. J.

(3) Price and Dickman, *Ind. and Eng. Chem.*, **40**, 257 (1948).

TABLE I

β -CHLOROVINYL KETONES, $\text{RCOCH}=\text{CHCl}$												
R	R'	Yield, %	$^{\circ}\text{C.}$	B. p. Mm.	n_D^{25}	d_4^{25}	Obs. MR	Calcd.	%C Found	%H Found	%C Calcd.	%H Calcd.
Methyl ^a	62	41	21	1.4654 ²⁰	1.130 ²⁰	25.6	25.08				
Isobutyl ^b	66	53	0.6				
Isoamyl ^c	65	108	30	1.4619	0.993	47.8	46.0	59.74	8.25 ^d	59.81	8.16
Isohexyl ^d	80	64 110	1 20	1.4600	0.975	49.4	48.1	62.12	8.90	61.88	8.66
β -Ketoacetals, $\text{RCOCH}_2\text{CH}(\text{OCH}_3)_2$												
Methyl	81	38	2.0	1.4139	0.9895	33.35	32.97				
Isobutyl	90	81	7	1.4204	.939	17.0	47.07	61.97	10.52	62.04	10.41
Isoamyl	80	124	25	1.4260	.932	51.6	51.68	63.58	10.36	63.79	10.71
Isohexyl	84	97	3	1.4300	.925	56.5	56.30	65.25	11.00	65.30	10.96
β -Hydroxyacetals, $\text{R}'\text{C}(\text{OH})\text{CH}_2\text{CH}(\text{OCH}_3)_2$												
Isobutyl	Methyl	65 ^f	98	10	1.4310	0.928	53.4	53.2	63.44	11.61	63.11	11.65
Isoamyl	Methyl	59 ^g	121	17	1.4332	.917	57.9	57.82	64.47	11.95	64.66	11.82
Isohexyl	Methyl	56.5 ^h	83	0.8	1.4364	.918	62.6	62.44	65.74	12.01	66.01	12.05
Isobutyl	Allyl	70	130	20	1.4465	.936	61.7	61.97	66.95	11.26	66.63	11.14
α,β -Unsaturated Aldehydes, $\text{RC}=\text{CHCO}$ CH_3												
Isobutyl ⁱ	51	65	10	1.4579	0.860	40.0	38.7	74.64	11.01	76.14	11.19
Isoamyl ^j	60	82.5	9	1.4625	.862	44.7	43.32	77.03	11.43	77.09	11.50
Isohexyl	52	73	1	1.4611	.859	49.9	47.93	77.66	11.73	77.87	11.76

^a This ketone solidifies at approx. 5° and is much more stable in solid form. Yakubovich and Merkulova⁷ report b. p. 38–39° (18–20 mm.), n_D^{20} 1.4683, d_4^{20} 1.9858. ^b Carpmals⁸ reported b. p. 63–65° (12 mm.). ^c 2,4-Dinitrophenylhydrazones, golden-orange platelets from ethanol, m. p. 118–119°. *Anal.* Calcd. for $\text{C}_{14}\text{H}_{17}\text{ClN}_4\text{O}_4$: C, 49.34; H, 5.03; Cl, 10.41; N, 16.44. Found: C, 49.58; H, 5.04; Cl, 10.22; N, 16.23. ^d 2,4-Dinitrophenylhydrazone, m. p. 112–112.5°, cor. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{19}\text{ClN}_4\text{O}_4$: C, 50.78; H, 5.50; Cl, 10.24; N, 15.86. Found: C, 50.94; H, 5.39; Cl, 10.00; N, 15.79. ^e Calcd.: Cl, 21.87. Found: Cl, 22.07. ^f A second fraction was obtained in 10% yield, b. p. 60–62° (10 mm.); n_D^{25} 1.4224, d_4^{25} 0.898. ^g A 15% yield of a second fraction was identified as 3,6-dimethyl- Δ^3 -heptenal dimethyl acetal, b. p. 83–86° (14 mm.); n_D^{25} 1.437; d_4^{25} 0.879; $MR_{\text{obs.}}$ 55.5; $MR_{\text{calcd.}}$ 55.83. *Anal.* Calcd. for $\text{C}_{11}\text{H}_{22}\text{O}_2$: C, 70.85; H, 11.81. Found: C, 70.84; H, 12.32. Assignment of the location of the double bond is based on hydrolysis to the unsaturated aldehyde, n_D^{25} 1.444; for the conjugated unsaturated aldehyde, n_D^{25} 1.462. ^h From this experiment, a 4% yield of a second fraction was obtained, b. p. 57° (0.8 mm.), n_D^{25} 1.4414, d_4^{25} 0.839. Found: C, 76.55; H, 12.92. ⁱ Semicarbazone; m. p. 151.7–152.5, cor. *Anal.* Calcd. for $\text{C}_9\text{H}_{17}\text{N}_3\text{O}$: C, 58.99; H, 9.35; N, 22.90. Found: C, 58.78; H, 8.87; N, 22.11. ^j Semicarbazone, m. p. 164.3–164.6°. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{19}\text{N}_3\text{O}$: C, 60.88; H, 9.71; N, 21.29. Found: C, 60.72; H, 9.53; N, 21.19.

β -ketobutyraldehyde), evolved hydrogen and heat on treatment with sodium, and did not react with sodium sulfite.

β -Hydroxyacetals.—The Grignard reagent (*ca.* 0.80 mole) was prepared in ether and the ketoacetal (*ca.* 0.60 mole) added with stirring at 20°. After hydrolysis in cold aqueous ammonium acetate, the dried ether extract was distilled, with a pinch of potassium carbonate added. In every experiment, some low-boiling material, evidently corresponding to dehydration to an unsaturated acetal, was obtained.

α,β -Unsaturated Aldehydes.—Numerous experiments on various conditions for hydrolysis and dehydration, including potassium acid sulfate, and hydrochloric acid, were investigated but distillation from oxalic acid proved most satisfactory. The acetal (0.3 mole) was added dropwise to a 50-ml. modified Claisen flask containing 5 g. of anhydrous oxalic acid and 0.5 g. of hydroquinone heated in an oil-bath at 85–95° and maintained under 1 mm. pressure. The distillate so obtained was then redistilled.

The nine- and ten-carbon aldehydes had pleasant,

lemon-like odors and flavors, but the eight-carbon homolog had a somewhat harsh, mint-like odor.

Attempted conversion of the isobutylallylcarbinol to α,β -unsaturated aldehyde failed to give the desired product. In this molecule, as in citral, there is a double bond so situated that the aldehyde carbonyl group can undergo an internal Prins-type condensation, which presumably accounts for its sensitivity to the acid conditions necessary for hydrolysis and dehydration.

The ultraviolet spectra of citral and 6,7-dihydrocitral (3,7-dimethyl- Δ^2 -octenal) were compared in ethanol solution. Each showed two maxima, citral at 2390 Å., $\epsilon = 1.42 \times 10^4$ and at 3200 Å., $\epsilon = 65.8$, and dihydrocitral at 2395 Å., $\epsilon = 1.42 \times 10^4$ and at 3200 Å., $\epsilon = 56.4$.

A 0.5-g. sample of 3,6-dimethyl- Δ^2 -heptenal and 0.55 g. of potassium carbonate in 6 ml. of water were boiled under reflux for five hours. Vapors escaping from the reflux condenser were passed into ice-cold alcohol. The alcohol solution yielded acetaldehyde 2,4-dinitrophenylhydrazone, m. p. 156–158°. The decomposition to acetaldehyde is similar to that for citral,¹⁰ and the melting point of the derivative corresponds to that reported by Verley, m. p. 156–157°.

Decomposition of Dihydrocitral in Aqueous Solution.—The rate of decomposition of dihydrocitral in acidic aqueous solution was compared to that of citral by measure-

(9) Theimer and Ritter (Abstracts, Organic Division, 110th Meeting, American Chemical Society, Chicago, Ill., Sept., 1946) reported the preparation of citral by a similar scheme using the cyclic acetal of β -ketobutyraldehyde with 2-methyl-2,4-pentanediol. This 1,3-dioxane-type acetal is, however, not readily hydrolyzed to the parent aldehyde.

(10) Verley, *Bull. soc. chim.*, 3, 17 (1897).

ment of disappearance of unsaturation and of carbonyl content.³ The reaction mixtures were prepared by adding 0.2 g. of aldehyde in 25 ml. of ethanol to 950 ml. of water and enough dilute hydrochloric acid to make the solution $1.8 \times 10^{-3} N$ in hydrochloric acid. Unsaturation was followed by bromine titration, carbonyl content by reaction with hydroxylamine sulfate, titrating the liber-

ated acid to pH 4.02 with 0.01 *N* barium hydroxide. Because of the high dilution of the dihydrocitra, the accuracy in the titrations was not better than about $\pm 3\%$. The results are summarized in Tables II and III.

The rates of disappearance of citral are in agreement with the rate predicted from the rate constant at 45° as measured by Price and Dickman.³ As expected from the mechanism they proposed for citral and citronellal, the rate for dihydrocitra is much less, especially as measured by the disappearance of carbonyl. The difference in carbonyl and unsaturation titers for the dihydrocitra is unquestionably due to equilibrium hydration of the double bond conjugated to the aldehyde. If this be the explanation, the rate of hydration is considerably more rapid than for crotonaldehyde⁴ and the equilibrium is slightly more favorable to the unsaturated aldehyde. Both these differences would be expected since in this case the product of hydration would be a tertiary, rather than a secondary, alcohol. The reason for the slow disappearance of the aldehyde group was not determined although the ease of oxidation and aldolization of aldehydes does not make it appear unreasonable.

Summary

A procedure has been described for the synthesis of several α,β -unsaturated aldehydes involving (a) addition of acyl chlorides to ketones to form β -chlorovinyl ketones, (b) reaction with methanolic alkali to form β -keto acetals, (c) dehydration of the hydroxy acetals over oxalic acid.

By this scheme, "dihydrocitra" was prepared and was shown to be far more stable in dilute aqueous acid than either citral or citronellal.

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TABLE II
RATE OF DISAPPEARANCE OF DIHYDROCITRAL AT 45° IN
 $1.8 \times 10^{-3} N$ HYDROCHLORIC ACID

Time	Unsaturation, ^a %	Aldehyde, ^b %
0	100	100
24	69	89
48	55	86
62	50	...
72	...	90
84	48	...
240	43	64
2304	...	49

^a By bromine titration. ^b By reaction with hydroxylamine sulfate.

TABLE III
RATE OF DISAPPEARANCE OF CITRAL AT 45° IN $1.8 \times 10^{-3} N$
HYDROCHLORIC ACID

Time	Unsaturation, ^a %	Aldehyde, ^b %
8	49	53
48	12	24

^a By bromine titration based on disappearance of only one of the two double bonds of citral. ^b By hydroxylamine sulfate.

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Studies of Some Characteristics of Vitamin B_{12b}

By J. V. PIERCE, A. C. PAGE, JR., E. L. R. STOKSTAD AND T. H. JUKES

Introduction

The crystallization of vitamin B_{12b}, a biologically active substance related to vitamin B₁₂, was described previously.¹ The present communication describes further properties of the compound.

The crystalline vitamin was prepared from *Streptomyces aureofaciens* fermentation as before¹ and was dried at room temperature in a vacuum desiccator over phosphorus pentoxide. This procedure left about 6% of residual "moisture" which could be removed by heating at 100°; however, the data to be reported were obtained with unheated preparations.

The absorption spectra of vitamins B₁₂ and B_{12b} in ultraviolet and visible light are compared in Fig. 1. Average analyses² of two samples showed the cobalt content to be 3.64% and the phosphorus content 2.0%, corresponding to a

molecular weight of about 1500 on a moisture-free basis.^{2a}

Infrared absorption spectra in mineral oil suspension were measured on both single beam and per cent. transmission instruments.³ It was found that an absorption band at 2140 cm.⁻¹ exhibited by vitamin B₁₂ was not shown by vitamin B_{12b}. An attempt to measure the refractive indices failed due to the opacity of the crystals.

The biological activity of vitamin B_{12b} for *Lactobacillus leichmannii* 313 and for chicks was found to be approximately the same as that of vitamin B₁₂.

Experimental

An aqueous solution of vitamin B_{12b}, 50 micrograms per ml., was examined in a Beckman spectrophotometer

(2a) More recent observations with thoroughly dried samples of vitamin B_{12b} have resulted in values of 4.4% to 4.6% for cobalt and extinction coefficients ($E_{1\%}^{1\text{cm}}$) of 136 at 274 $m\mu$, 167 at 351 $m\mu$ and 57 at 525 $m\mu$ (J. A. Brockman, Jr., and J. V. Pierce, unpublished data).

(3) By Dr. R. C. Gore, Stamford Research Laboratories, American Cyanamid Company.

(1) J. V. Pierce, A. C. Page, Jr., E. L. R. Stokstad and T. H. Jukes, THIS JOURNAL, 71, 2952 (1949).

(2) Carried out by Mr. Paul Giesecke, Stamford Research Laboratories, American Cyanamid Company; see P. Giesecke, Trans. Am. Inst. Mining and Metallurg. Engineers, 169, 706 (1946).