[Contribution from Goessmann Chemistry Laboratory, University of Massachusetts]

ACYLATION STUDIES. II. THE CONDENSATION OF γ-BUTYROLACTONE AND γ-VALEROLACTONE WITH METHYL KETONES[1]

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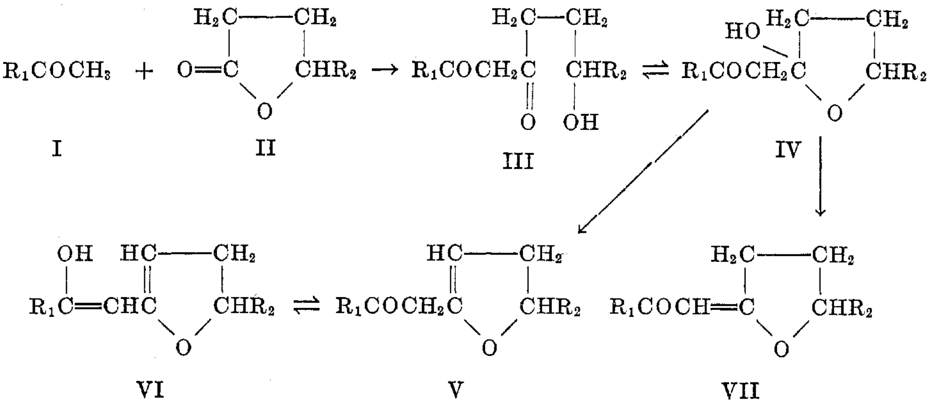
Lactones are cyclic esters known to undergo a number of reactions typical of ordinary esters, but there appears to be only one report[4] of a reaction in which a lactone serves as an acylating agent. The condensation of two such cyclic esters, γ-butyrolactone and γ-valerolactone, with methyl ketones to give 2-(2-hydroxyl-1-alkenyl)-4,5-dihydrofurans (VI) in 32–59% yields is reported in this paper.

The reactions were effected with the basic catalyst sodium amide. Purification of the crude reaction products by the copper salt method was not generally satisfactory. However, copper salts were obtained from most of the crude products, and they gave satisfactory analyses for the salts of compounds with structure III. The materials regenerated from the copper salts of the crude products IIIaA and IIIhB gave both positive iodoform tests and positive enol tests with ferric chloride. On reaction with 2,4-dinitrophenylhydrazine, they yielded prod-



R_1 = (a) CH_3, (b) C_2H_5, (c) n-C_3H_7, (d) iso-C_3H_7, (e) cyclo-C_3H_5, (f) iso-C_4H_9, (g) n-C_5H_{11}, (h) C_6H_5.
R_2 = (A) H, (B) CH_3.

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[4] An enol-lactone, diethyl 2-butanolidene-malonate, was converted to succinyldimalonic ester by reaction with diethyl malonate in the presence of sodium [Ruggli and Maeder, *Helv. Chim. Acta*, **26**, 1476 (1943)]. This can be considered a reaction in which the lactone serves as an acylating agent in a manner similar to that of an ester in a Claisen-type acylation.

Recently the reaction of β-propiolactone with a number of active methylene compounds ucts which analyzed satisfactorily for the 2,4-dinitrophenylhydrazones of IIIaA and IIIhB. These results were considered evidence that the initial reaction products were γ-hydroxy-1,-3-diketones (III).

After purification by fractionation, the products gave much stronger tests for enols with ferric chloride, but they did not form 2,4-dinitrophenylhydrazones. The acetophenone product no longer gave an iodoform test. In fact, only the products derived from acetone (Ia) gave positive iodoform tests, whereas all products with structure IIIB would be expected to form iodoform. Solid acetate and benzoate derivatives were not obtained, but the oils obtained from the acetylations and benzoylations gave negative enol tests. Analyses of the products indicated that the loss of one molecule of water from III had occurred.

It has been shown (1) that a number of γ-hydroxy aldehydes and γ-hydroxy ketones exist as equilibrium mixtures of the straight-chain and the cyclic hemiacetal forms. This is known as ring-chain tautomerism (2). Distillation of δ-phenyl-γ-methyl-γ-hydroxyvaleraldehyde results in the loss of a molecule of water to form 2-methyl-2-benzyl-2,3-dihydrofuran (1d). γ-Hydroxy ketones appear to be especially prone to lose water and form the "anhydride", the corresponding dihydrofuran, on heating (3). These apparently general properties of γ-hydroxy ketones offer an explanation of the observations in the present work. Dehydration of the tetrahydrofuran tautomers (IV) of the γ-hydroxy-1,3-diketones (III) during distillation would result in either V or VII. The behavior of the products suggests that the dehydration results in the dihydrofurans (V) which exist largely (if not entirely) as the enols (VI). The enols (VI) should be more stable since they contain a conjugated system.

Additional evidence for the enol structure (VI) was obtained from the molar refractions and their exaltations for the liquid γ-butyrolactone products. Hughes and Johnson (4) found that furan derivatives could be divided into two categories: one in which the average for EMR was −0.479 (furan and its derivatives which do not contain a double bond on the atom immediately attached to the ring in the α-position), and a second in which the average for EMR was +2.313 (furan derivatives with a side chain which contains a double bond conjugated with the ring). The average for EMR for five tetrahydrofuran derivatives was −0.14. The dihydrofurans in the present work would be expected to have somewhat lower exaltations than the furan derivatives, since they have two conjugated double bonds as compared to three in the furan derivatives. It is apparent from Table I that the observed molar refractions are in closest agreement with those calculated for the enol structure (VI) and that the exaltations are of the expected order of magnitude.

With certain of the unsymmetrical ketones used the condensation might occur at the α-methyl and/or α-methylene groups. All of the methylene derivatives

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has been reported [Gresham, Jansen, Shaver, Frederick, and Beears, *J. Am. Chem. Soc.*, **73,** 2345 (1951)]. However, most of the reactions were carried out in aqueous solution, and in every case the reaction effected was carbon *alkylation.* Preliminary work with β-propiolactone in this laboratory indicates that small amounts of acylation products may be obtained.

would be expected to give a positive iodoform test. The failure to obtain iodoform from any of the products except those derived from acetone indicates that in each case the product isolated was the methyl derivative.

It has been found (6) that the yields realized from acylations of ketones with esters and two equivalents of sodium amide are twice those obtained when one equivalent of the base is used. The explanation for this is that in order to obtain favorable equilibria a third step in which the product (IX) is converted to its enolate (X) is necessary. However, in the lactone-acetophenone condensations, the presence of sodium amide in excess of one equivalent had no significant effect on the yields (Table II). In step 2 of an ester-ketone condensation, the loss of an alkoxide ion results in the formation of the 1,3-diketone (IX). In the corresponding step of a lactone-ketone condensation, a separate alkoxide ion is not formed, since the diketone (XI) is itself the alkoxide ion. If this alkoxide ion (XI) is a stronger base than the enolate ion (XII), the enolate ion (which is

TABLE I

MOLAR REFRACTIONS[a] AND EXALTATIONS OF γ-BUTYROLACTONE CONDENSATION PRODUCTS

R_1	MR_D (V)	MR_D (VII)	MR_D (VI)	MR_D (OBS.)	EMR_D[b]
CH_3	33.908	33.872	34.736	36.576	1.840
C_2H_5	38.386	38.350	39.384	40.240	0.856
n-C_3H_7	43.034	42.998	44.032	44.460	0.428
iso-C_4H_9	47.682	47.646	48.680	49.444	0.764

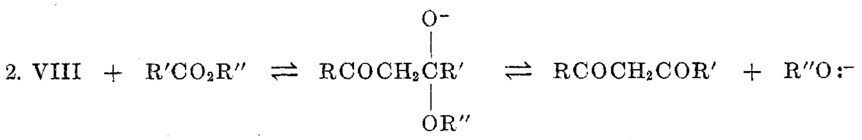
[a] MR_D were calculated using Vogel's values (5) for bond refractions. [b] $EMR_D = MR_D$ (Obs.) $- MR_D$ (VI).

TABLE II

EFFECT OF EXCESS SODIUM AMIDE ON THE YIELDS OF VIhA AND VIhB

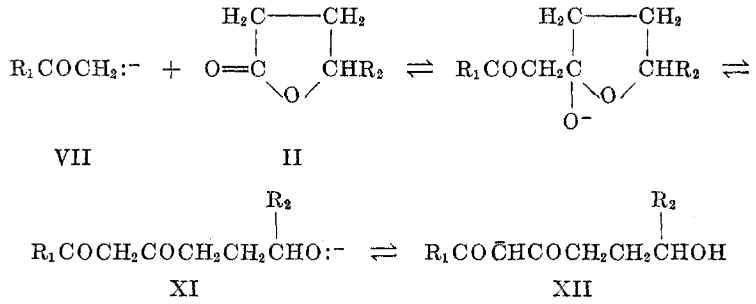
SODIUM AMIDE (equiv.)	YIELDS, %	
	VIhA	VIhB
1.0	31.8	51.6
1.5	28.2	48.1
2.0	27.6	56.3

$$1.\ RCOCH_3 + :NH_2^- \rightleftharpoons \underset{\text{VIII}}{RCOCH_2:^-} + NH_3$$



$$2.\ \text{VIII} + R'CO_2R'' \rightleftharpoons RCOCH_2\overset{O^-}{\underset{OR''}{C}}R' \rightleftharpoons \underset{\text{IX}}{RCOCH_2COR'} + R''O:^-$$

$$3.\ \text{IX} + :NH_2^- \rightleftharpoons \underset{\text{X}}{RCO\bar{C}HCOR'} + NH_3$$



analogous to ion X formed in step 3 of an ester-ketone condensation) would be the expected product of step 2 of a lactone-ketone condensation. Actually, the formation in step 2 of the sodio derivative of either ion XI or ion XII may displace the equilibria of all of the reactions in favor of the condensation product so that reaction with a second equivalent of base is not necessary to obtain maximum yields.

If the reaction is general for a variety of both lactones and active hydrogen compounds, it affords a method for the preparation of types of compounds not always readily available by other routes. The investigation of a number of these is in progress.

EXPERIMENTAL[5]

The authors are indebted to the General Aniline & Film Corp., Easton, Pa. and the Cliffs Dow Chemical Co., Marquette, Mich. for very generous samples of γ-butyrolactone.

The powdered sodium amide (purchased from Farchan Research Laboratories, Cleveland, Ohio) was stored, weighed, and transferred in a nitrogen atmosphere.

All reactants were dried over a suitable reagent. The dried reactants and the products were fractionated through a 2.5 x 30 cm. column packed with glass helices and equipped with a total condensation variable reflux ratio distilling head. Reactants boiling over a one-degree range were used.

General procedure. In a one-liter three-necked flask equipped with a glass sweep stirrer, a reflux condenser, and a 100-ml. dropping-funnel there was placed 300–400 ml. of anhydrous ether and 19.5 g. (0.5 mole) of sodium amide.[6] The flask was immersed in a water bath (20–25°). The ketone (0.5 mole) was added dropwise at a rate such that the evolution of ammonia was not too rapid (20–30 minutes), and the mixture was agitated for an additional 10 minutes after the addition was completed. The lactone (0.5 mole) in 100 ml. of anhydrous ether was then added (30 minutes), and the reaction mixture was refluxed on a water-bath for eight hours.

The mixture was cooled and ice (100 g.) was added (sodium amide reacts violently with water, so the addition must be done with caution especially when excess amide is used!). Enough water was added to dissolve the sodio derivatives and the ether layer was separated.[7] The aqueous layer was acidified with cold 50% sulfuric acid, the organic layer was separated, and the aqueous layer was extracted with successive 100-ml. portions of ether

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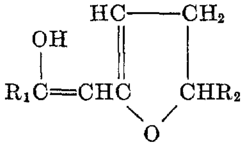
[5] Melting points and boiling points are uncorrected.

[6] In several runs in which the sodium amide was prepared in the reaction flask from sodium and liquid ammonia (6), the yields were essentially the same as those obtained with the commercial powdered sodium amide.

[7] Most of the unreacted ketone could be recovered by fractionation of this extract.

TABLE III

LACTONE-KETONE CONDENSATION PRODUCTS



R_1	R_2[a]	B.P., °C./4 MM.	YIELD, %	n_D^{25}	d_4^{25}	FORMULA	ANALYSES			
							C		H	
							Calc'd	Found	Calc'd	Found
CH_3[b]	H	80–81	23.8[c] 33.9[d]	1.5041	1.0215	$C_7H_{10}O_2$	66.64	66.52	7.99	7.90
C_2H_5[e]	H	85–86	35.0 43.0[f]	1.5014	1.0271	$C_8H_{12}O_2$	68.54	68.40	8.63	8.46
n-C_3H_7	H	87–88[g]	37.8	1.4888	1.0060	$C_9H_{14}O_2$	70.09	69.90	9.15	8.90
iso-C_4H_9	H	105–107	38.2	1.4878	0.9798	$C_{10}H_{16}O_2$	71.39	71.35	9.59	9.41
n-C_5H_{11}	H	118–119[h]	37.4			$C_{11}H_{18}O_2$	72.48	72.30	9.95	9.81
C_6H_5[i]	H	179–180[j]	31.8[k] 28.2[l] 27.6[m] 12.0[n]			$C_{12}H_{12}O_2$	76.57	76.45	6.43	6.39
CH_3	CH_3	79–80	46.5	1.492		$C_8H_{12}O_2$	68.54	68.75	8.63	8.70
C_2H_5	CH_3	90–91	45.9	1.485		$C_9H_{14}O_2$	70.09	69.95	9.15	9.16
n-C_3H_7	CH_3	101–102	34.6	1.487		$C_{10}H_{16}O_2$	71.39	71.60	9.59	9.72
iso-C_3H_7	CH_3	97–98	47.7	1.483		$C_{10}H_{16}O_2$	71.39	71.50	9.59	9.71
cyclo-C_3H_5[o]	CH_3	94–95	41.9	1.434		$C_{10}H_{14}O_2$	72.29	72.19	8.49	8.65
iso-C_4H_9	CH_3	111–112.5	59.3	1.484		$C_{11}H_{18}O_2$	72.48	72.60	9.95	9.84
n-C_5H_{11}	CH_3	124–125	36.2	1.478		$C_{12}H_{20}O_2$	73.42	73.70	10.27	10.34
C_6H_5	CH_3	159–160	51.6[k] 48.1[l] 56.3[m]	1.575		$C_{13}H_{14}O_2$	77.20	77.40	6.98	6.92

[a] The γ-butyrolactone (R_2 = H) and γ-valerolactone (R_2 = CH_3) condensations were effected with 1.25 equiv. and 1.0 equiv. of sodium amide, respectively, except where otherwise noted. [b] Diacetone alcohol, characterized as *mesityl oxide 2,4-dinitrophenylhydrazone*, m.p. 200–201° (7) and isophorone, *semicarbazone*, m.p. 187–189° (8) were also formed by self-condensation of the ketone. Heating of the reaction mixture before addition of the lactone resulted in increased amounts (up to 50% yield of isophorone) of the self-condensation products. [c] This product is very soluble in water and repeated extraction with ether was necessary. [d] This yield was obtained by isolation and purification *via* the copper salt. [e] Some material, believed to be ketone self-condensation products (9), was also isolated. [f] Two equiv. of lactone were used. [g] M.p. 13°. [h] M.p. 28.5°. [i] Dypnone, *semicarbazone*, m.p. 147–149° (10) was also obtained. [j] M.p. 41°. [k] Used 1 equiv. of sodium amide. [l] Used 1.5 equiv. of sodium amide. [m] Used 2.0 equiv. of sodium amide. [n] Benzene used as a solvent. Dypnone isolated in 6.7% yield. [o] Acetate acid (50%) was used to acidify the reaction mixture.

until the ether remained clear. The organic layer and ether extracts were combined, washed with two 100-ml. portions of 5% sodium bicarbonate solution, and the ether was removed under reduced pressure. The crude product was then fractionated. If water formed slowly during the distillation, the crude product was heated under total reflux for some time before fractionation was begun. The results of all of the condensations are presented in Table III.

Isolation of γ-hydroxy-1,3-diketones as copper salts. The reaction was carried out according to the general procedure. At the end of the 8-hour reflux, acetic acid (0.5 mole) in 100 ml. of water was added. Then a saturated cupric acetate solution (0.5 mole) was added. The copper salt was obtained by distillation of the solvent. If the salt did not form or separated as an oil, the mixture was allowed to stand in a refrigerator until crystallization occurred.

Formation of copper salts from crude γ-hydroxy-1,3-diketones (III). The crude product (5 g.) was dissolved in an equal volume of methanol, and 30 ml. of warm (70°) saturated cupric acetate solution was added. The salt usually formed immediately but the mixture was allowed to stand to obtain complete precipitation. Most of the salts were recrystallized from ethanol-water or methanol-water mixtures. In certain cases acetone, benzene, ether, or petroleum ether were more satisfactory solvents. Data for the copper salts are given in Table IV.

TABLE IV

COPPER SALTS OF γ-HYDROXY-1,3-DIKETONES (III)

R_1	R_2	M.P., °C.	FORMULA	ANALYSES					
				C		H		Cu[a]	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_3	H	134–136	$C_{14}H_{22}CuO_6$	48.06	47.80	6.20	5.96	18.17	17.92
C_2H_5	H	125–126.5	[b]						
n-C_3H_7	H	139.5–141	[b]						
iso-C_4H_9	H	137–138	$C_{20}H_{34}CuO_6$	55.34	55.20	7.90	7.81	14.64	14.26
n-C_5H_{11}	H	129–130	$C_{22}H_{38}CuO_6$	57.19	56.92	8.29	8.03	13.75	13.48
C_6H_5	H	141–143	[b]						
CH_3	CH_3	124	$C_{16}H_{26}CuO_6$	50.84	50.30	6.93	7.61	16.81	16.79
C_2H_5	CH_3	141–141.5	$C_{18}H_{30}CuO_6$	53.25	52.87	7.45	8.00	15.65	15.60
n-C_3H_7	CH_3	97.5–98.5	$C_{20}H_{34}CuO_6$	55.34	55.30	7.90	8.50	14.64	14.40
iso-C_3H_7	CH_3	116.5–117.5	$C_{20}H_{34}CuO_6$	55.34	54.93	7.90	8.46	14.64	14.60
cyclo-C_3H_5[c]	CH_3								
iso-C_4H_9	CH_3	120	$C_{22}H_{38}CuO_6$	57.19	56.84	8.29	8.77	13.75	13.60
n-C_5H_{11}[d]	CH_3								
C_6H_5	CH_3	151	$C_{26}H_{30}CuO_6$	62.20	62.10	6.02	6.58	12.66	12.45

[a] Copper was determined as CuO, the residue remaining after combustion of the sample for carbon-hydrogen analysis. [b] This salt was not analyzed. [c] A copper salt did not form. [d] The copper salt could not be recrystallized.

Recovery of γ-hydroxy-1,3-diketones (III) from copper salts. The copper salt was dissolved in an excess of 15% sulfuric acid. This was then extracted with ether and the ether extracts were combined and dried. The γ-hydroxy-1,3-diketones (III) were obtained by evaporating without heating the ether under an air-jet. They were converted to the 2,4-dinitrophenylhydrazones by the usual procedure (11).

The *2,4-dinitrophenylhydrazone* of 7-hydroxy-2,4-heptadione (IIIaA) melted at 75–77°.

Anal. Calc'd for $C_{13}H_{14}N_4O_5$: C, 50.96; H, 4.61.

Found: C, 51.10, H, 4.40.

The *2,4-dinitrophenylhydrazone* of 7-hydroxy-1-phenyl-1,3-heptadione (IIIhB) melted at 239–240°.

Anal. Calc'd for $C_{19}H_{20}N_4O_6$: C, 56.99; H, 5.04.

Found: C, 56.75; H, 4.79.

SUMMARY

The acylation of methyl ketones with γ-butyrolactone and γ-valerolactone yields γ-hydroxy-1,3-diketones, whose hemiacetal tautomers lose water during distillation. The products, 2-(2-hydroxy-1-alkenyl)-4,5-dihydrofurans, are obtained in 32–59% yields.

In contrast to ester-ketone condensations, maximum yields are obtained in the lactone-ketone condensations with only one equivalent of base. This is explained by the accepted mechanism for base-catalyzed condensations.

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