Self-Condensation of α-Keto Esters under Stobbe Condensation Conditions[1]

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Stobbe condensations have been run successfully on γ-[3] and δ-keto esters[4] to give the expected products. With β-keto esters only products resulting from cleavage of the keto ester were formed.[5] No mention could be found in the literature, however, of the use of α-keto esters or acids in this reaction. In light of the reported successful base-catalyzed mixed aldol condensations between aldehydes and ketones and pyruvic acid,[6] phenylpyruvic acid,[7] and ethyl pyruvate,[8] it was felt that no difficulty should be encountered in the use of α-keto esters in the Stobbe reaction. Since the expected products from such condensations were considered to be interesting and useful synthetic intermediates, a study of the reaction was initiated.

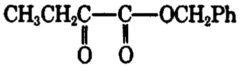
Attempted condensation of benzyl α-ketobutyrate (**1**) with di-*t*-butyl succinate in the presence of potassium *t*-butoxide gave, after work-up, a five-component mixture. Almost the entire amount of succinate was recovered as di-*t*-butyl succinate, *t*-butyl hydrogen succinate, and *t*-butyl benzyl succinate. The two remaining acidic materials, A and B, were separated chromatographically.

Similar results with somewhat higher yields were obtained using an excess of sodium hydride as the condensing agent but, in the presence of 0.1 equiv of this base a third acidic material, C, was obtained. Since the same general results were obtained in the absence of succinate, self-condensation of the keto ester was indicated. Reaction of either benzyl or ethyl pyruvate under these conditions (in the presence or absence of succinate) gave a material which was identical with the substance obtained from the base-catalyzed self-condensation of pyruvic acid and to which the lactonic acid structure, **3a**, has been assigned.[9]

Tentative identification of A as **2a** was based on the analogy with the formation of **3a** from pyruvic acid as well as on its elemental analysis and ultraviolet [λ_{max} 241 mμ (ε 25,580)]; infrared [3260 (OH), 1750 (γ-lactone), 1732 (CO_2H), 1670 cm^{-1} (C=C)]; and nmr spectra [δ 0.88 + 2.10 (CH_3–CH_2–); 1.89 ($>C{=}C{-}CH_3$); 7.13 ($>C{=}C{-}OH$)]. Compounds B and C were considered to be the *t*-butyl and benzyl esters, respectively, of **2a** on the basis of their elemental analyses, their interconversion with **2a**, and their nmr spectra [δ 1.47 (*t*-butyl ester in **2b**) and 5.20 and 7.32 (benzyl ester in **2c**) in addition to the peaks observed in the spectrum of **2a**].

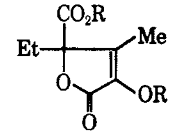
Examination of the literature, however, revealed that the structure of **3a** was not unequivocally assigned. Since the ψ acid **4** would also be expected to exhibit the spectral and chemical[10] characteristics observed with compound A, and since both structures represent potential self-condensation products from **1**, it was felt that it was necessary to differentiate between these two possible structures for A. In order to accomplish this, A was treated with diazomethane. If A were the ψ acid **4**, it would be expected to give a keto ester[11] while if it were the hydroxy lactone **3a**, it should give an enol ether ester. The product obtained from this reaction was the enol ether **2d**, and compound **3a** gave the enol ether **3b** as shown by the nmr spectra of the products. (See Experimental Section.) Thus, the assigning of the hydroxy butenolide structures, **2** and **3**, to the self-condensation products obtained from the α-ketobutyric and pyruvic esters was verified.

It should be noted that no self-condensation products were reported to be formed in the base-catalyzed mixed aldol condensations involving α-keto acids or esters.[6–8,12] In the acid-catalyzed mixed aldol condensation of phenylpyruvic acid, however, some hydroxy butenolide formation was observed.[7]

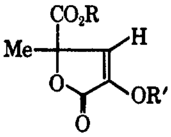


$$\mathrm{CH_3CH_2\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-OCH_2Ph}$$

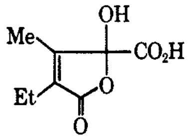
1



2a, R = H; R′ = H
b, R = *t*-Bu; R′ = H
c, R = CH_2Ph; R′ = H
d, R = Me; R′ = Me



3a, R = R′ = H
b, R = R′ = Me



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Experimental Section[13]

Benzyl α-Ketobutyrate (1).—A mixture of 25.5 g (0.25 mole) of α-ketobutyric acid,[14] 32.4 g (0.30 mole) of benzyl alcohol and 100 ml of dry benzene was refluxed through a Dean–Stark water separator for 17 hr. Evaporation of the benzene produced a viscous oil which on distillation gave 31.6 g (66%) of a pale yellow liquid: bp 129–131° (7 mm); $n^{20}D$ 1.5083; infrared, 1730 (ester CO), 1400 ($-CH_2-CO$), 1380 ($C-CH_3$) and 690 cm^{-1} (monosubstituted phenyl); nmr (neat), 5 H singlet at δ 6.78 (phenyl), 2 H singlet at 4.67 ($O-CH_2$), 2 H quartet at 2.19 (CH_2-CH_3), and 3 H triplet at 0.508 (CH_2CH_3).

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(2) Taken, in part, from the dissertation submitted by L. P. C. to Seton Hall University (1966) in partial fulfillment of the requirements for the Ph.D. degree.

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Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.66; H, 6.23.

The **2,4-dinitrophenylhydrazone** was recrystallized from ethanol, mp 171–172°.

Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.84; H, 4.33; N, 15.05. Found: C, 54.91; H, 4.12; N, 14.93.

Stobbe Condensation. Benzyl α-Ketobutyrate in the Presence of Di-*t*-butyl Succinate. Potassium *t*-Butoxide Method.—A mixture of 10.0 g (0.052 mole) of keto ester **1** and 18.4 g (0.08 mole) of di-*t*-butyl succinate in 5 ml of dry *t*-butyl alcohol was added to a warm solution of potassium *t*-butoxide prepared by treating 2.6 g (0.067 g-atoms) of potassium metal with 46 ml of dry *t*-butyl alcohol. The addition of the ester mixture took 35 min and the reaction temperature was maintained at 70–80° for an additional 1.5 hr. Ether (25 ml) and water (20 ml) were added and the mixture stirred for 15 min. The layers were separated and the ether was washed with saturated sodium bicarbonate solution, dried, filtered, and evaporated leaving 20.6 g of an orange oil which did not form a 2,4-dinitrophenylhydrazone.

The aqueous layer and alkaline extracts were combined and acidified in the cold with 10% hydrochloric acid and extensively extracted with ether. The ether was dried, filtered, and evaporated leaving 4.5 g of an acidic oil which solidified on standing.

Distillation of the oil obtained from the neutral extracts gave two fractions: 8.0 g of di-*t*-butyl succinate, bp 55–60° (0.05 mm), and 8.0 g of viscous yellow liquid, bp 116–126° (0.05 mm), redistillation of which at 0.02 mm gave a pale yellow liquid (bp 99–100°, $n^{20}D$ 1.4862) which was identified as benzyl *t*-butyl succinate. Infrared (film) bands were at 1730 (ester CO), 1365 (*t*-butyl), 740 and 690 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.82; mol wt, 264.3. Found: C, 68.16; H, 7.63; mol wt, 250.

Gas chromatography of the acidic fraction showed the presence of three components (A:B:X) with relative per cent ratios of 16.2:68.7:15.1. Parts of the crude acidic mixture (1.5 g) were placed on a column containing 28 g of Woelm acid-washed alumina and eluted with 6 l. of a 9:1 petroleum ether (30–60°)–ether mixture giving 980 mg of component B. Recrystallization from pentane gave a white solid (mp 89.5–90.5°) which dissolved in sodium bicarbonate solution on standing, decolorized bromine–carbon tetrachloride solution, and did not form a precipitate when heated with 2,4-dinitrophenylhydrazine reagent; infrared bands were at 3520 sharp (O–H), 3340 broad (O–H), 1765 (γ-lactone), 1725 (ester CO), 1365 (*t*-butyl), and weak shoulder 1700 cm^{-1} (C=C tetrasubstituted); nmr ($CDCl_3$) showed 1 H broad at δ 7.13 (enol O–H), 2 H multiplet at 2.10 (methylene), 3 H singlet at 1.89 (vinyl methyl), 9 H singlet at 1.47 (*t*-butyl), and 3 H triplet at 0.88 (methyl). Component B was identified as α-hydroxy-β-methyl-γ-ethyl-$\Delta^{\alpha,\beta}$-butenolide-γ-carboxylic acid *t*-butyl ester (**2b**).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49; mol wt, 242.1. Found: C, 59.65; H, 7.40; mol wt, 236.

Further elution with 1 l. of a 4:1 ether–methanol mixture gave 440 mg of solid (A and X) which gave off carbon dioxide when treated with sodium bicarbonate solution.

Component X (200 mg) was separated from A by washing the chromatographed material several times with warm petroleum ether (bp 30–60°) and was shown to be identical in all respects, by comparison with an authentic sample, with *t*-butyl hydrogen succinate, mp 50–51° (lit.[15] mp 51–52°).

The petroleum ether insoluble solid A, mp 141–146°, was recrystallized from ether–pentane giving 200 mg of a white powder, mp 148–150°, which gave off carbon dioxide when treated with sodium bicarbonate solution, decolorized bromine–water solution, and gave a faint orange color with 1% ethanolic ferric chloride solution; infrared (nujol) bands were at 3260 (hydroxyl O–H), 2630 (carboxyl O–H), 1750 (γ-lactone), 1700 shoulder, 1732 (acid CO), and 1670 cm^{-1} (C=C); ultraviolet, λ_{max} 241 mμ (ε 25,580).

Component A did not form a precipitate even after refluxing overnight with 2,4-dinitrophenylhydrazine reagent. No precipitate was obtained from similar treatment with semicarbazide hydrochloride–sodium acetate or hydroxylamine hydrochloride–pyridine reagents.

Component A was identified as α-hydroxy-β-methyl-γ-ethyl-$\Delta^{\alpha,\beta}$-butenolide-γ-carboxylic acid (**2a**).

Anal. Calcd for $C_8H_{10}O_5$: C, 51.58; H, 5.42; mol wt, 186.1. Found: C, 51.64; H, 5.52; mol wt, 195.

The use of ethyl or benzyl pyruvate[16] or pyruvic acid in this reaction led to the formation of the butenolide, **3a**.[9]

Sodium Hydride Method. A.—A mixture of benzyl α-keto butyrate (6.0 g 0.031 mole) and di-*t*-butyl succinate (20.8 g, 0.09 mole) in 20 ml of dry benzene was added over a 45-min period to a stirred suspension of 2.16 g (0.09 mole) of sodium hydroxide in 20 ml of dry benzene. After hydrogen evolution subsided (about 1 hr) the contents were carefully acidified with glacial acetic acid. The reaction mixture was taken up in ether and the ether washed with saturated sodium carbonate solution until the washings were colorless. The ether was dried, filtered, and evaporated leaving 22.3 g of neutral oil, distillation of which gave 14.1 g of di-*t*-butyl succinate (68% recovery) and 5.4 g of benzyl *t*-butyl succinate.

Careful acidification of the cold basic extracts with 10% hydrochloric acid was followed by extraction with ether. The ether was dried, filtered, and evaporated giving 2.7 g of a dark oil which solidified on standing. Gas chromatographic analysis of the crude acidic mixture showed the presence of three components: 22.3%, A; 54.0%, B; 17.2%, X; and 6% of higher boiling material. Components A, B, and X, were shown to be identical with materials previously isolated from the potassium *t*-butoxide condensation reaction.

B.—Di-*t*-butyl succinate (46.0 g, 0.20 mole) was added to a stirred suspension of 1.44 g (0.06 mole) of sodium hydride in 10 ml of dry benzene. The flask was immersed in an ice bath and 10.0 g (0.052 mole) of benzyl α-keto butyrate added slowly. The mixture was then stirred at room temperature for 14 hr. Addition of 10 ml of water caused the precipitation of 5.3 g of a white solid which was filtered and washed with ether.

The combined ethereal filtrates were washed with saturated sodium bicarbonate solution, dried, filtered, and evaporated. Distillation of the residual oil (42.7 g) gave 39.3 g of di-*t*-butyl succinate (86% recovery).

Acidification of the bicarbonate extracts with 10% hydrochloric acid followed by extensive ether extraction and the usual work-up gave 1.0 g of a substance, mp 141–146°, identical in all respects with component A, obtained previously.

α-Hydroxy-β-methyl-γ-ethyl-$\Delta^{\alpha,\beta}$-butenolide-γ-carboxylic Acid Benzyl Ester (2c).—The white solid obtained from the sodium hydride procedure was dissolved in water. The basic solution was acidified with 2 *N* sulfuric acid and a cloudy suspension resulted which was extracted with ether. The ether was dried, filtered, and evaporated leaving a yellow oil which had a pleasant odor and solidified on standing, mp 67–76°. The solid decolorized bromine–carbon tetrachloride solution dissolved in sodium bicarbonate solution on standing and did not form a precipitate when refluxed with 2,4-dinitrophenylhydrazine reagent. Repeated recrystallization from pentane raised the melting point to 77–80° and final recrystallization from carbon tetrachloride gave large transparent plates: mp 79–80°; infrared, 3250 sharp (O–H), 3340 broad (O–H), 1765 (γ-lactone), 1730 (ester CO), and 690 cm^{-1} (monosubstituted phenyl); nmr, 5 H singlet δ 7.32 (phenyl), 1 H broad 6.54 (enol O–H), 2 H singlet 5.20 (O–CH_2–), 2 H multiplet 2.10 (CH_2–CH_3), 3 H singlet 1.86 (vinyl methyl), and 3 H triplet 0.88 (CH_2–CH_3).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.02; H, 5.69.

Hydrogenation of 2c.—The sodium salt of the enol of the γ-lactonic acid benzyl ester, **2c** (0.5 g, 0.0018 mole), was dissolved in 20 ml of 50% aqueous ethanol and added to 50 mg of 5% palladium-on-carbon catalyst. The mixture was hydrogenated for 1.5 hr at atmospheric pressure and room temperature. The catalyst was removed by filtration through Celite and the alcohol removed from the filtrate at reduced pressure. The remaining alkaline solution was acidified with 10% hydrochloric acid and extracted with ether. Evaporation of the ether gave 470 mg of a tan solid, mp 125–135°. Recrystallization from petroleum ether (30–60°) gave 330 mg (68%) of a white solid, mp 148–150°, identical in all respects with **2a**.

Methylation with Diazomethane.—The diazomethane was prepared from Diazald and collected by codistillation with ether according to the method of deBoer and Backer.[17]

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α-Methoxy-β-methyl-γ-ethyl-$\Delta^{\alpha\beta}$-butenolide-γ-carboxylic Acid Methyl Ester (2d).—A solution of 500 mg (0.0028 mole) of **2a** in 30 ml of ether was gradually added with swirling to an ether solution containing 360 mg (50% excess) of diazomethane. After standing for 3 hr the excess diazomethane was decomposed with 4 drops of glacial acetic acid. The ethereal solution was then washed with sodium bicarbonate solution to remove the acetic acid. The ether was dried, filtered, and evaporated leaving 510 mg of the enol ether methyl ester (**2d**). An analytical sample was isolated by preparative glpc: infrared (CCl_4), 1780 (γ-lactone), 1740 (ester CO) and 1680 cm^{-1} (C=C); nmr, 3 H singlet δ 3.97 (enol $-OCH_3$), 3 H singlet 3.74 (ester $-OCH_3$), 2 H multiplet 1.99 (methylene), 3 H singlet 1.80 (vinyl methyl) and 3 H triplet 0.87 (methyl); ultraviolet, λ_{max} 234 mμ (ε 7540).

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.21; H, 6.48.

α-Methoxy-γ-methyl-$\Delta^{\alpha,\beta}$-butenolide-γ-carboxylic Acid Methyl Ester (3b).—An ethereal solution of 350 mg (50% excess) of diazomethane was gradually added with shaking to a solution of 400 mg (0.0025 mole) of **3a** in 25 ml of ether until the yellow color persisted. The reaction mixture stood for 3 hr at room temperature after which time it was washed with saturated sodium bicarbonate solution. The ether was dried, filtered, and evaporated leaving 420 mg of a yellow oil. An analytical sample was isolated by preparative glpc: infrared (CCl_4), 1795 (γ-lactone), 1745 (ester CO) and 1660 cm^{-1} (C=C); ultraviolet, λ_{max} 230 mμ (ε 4740); nmr, 1 H singlet δ 6.12 (vinyl H), 3 H singlet 3.72 (enol $-OCH_3$), 3 H singlet 3.67 (ester $-OCH_3$), and 3 H singlet 1.61 (methyl).

Registry No.—**1**, 15023-79-7; **1** 2,4-dinitrophenylhydrazone, 15023-80-0; **2a**, 15023-81-1; **2b**, 15023-82-2; **2c**, 15023-83-3; **2d**, 15023-84-4; **3b**, 15023-85-5; di-*t*-butyl succinate, 926-26-1; benzyl *t*-butyl succinate, 15026-16-1; *t*-butyl hydrogen succinate, 15026-17-2.

Methylation of 10-Methyl-1(9)-octal-2-ones by Organocopper Reagents

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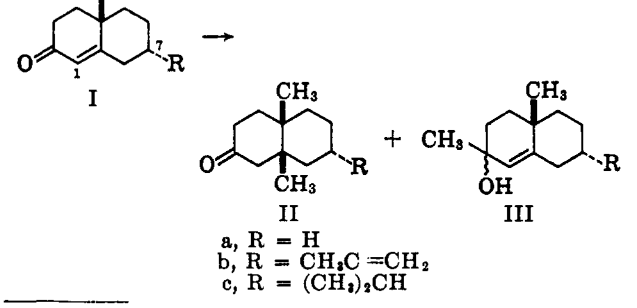
In connection with a project aimed at the synthesis of the naturally occurring sesquiterpene valeranone, we examined the stereochemistry of 1,4 additions to 10-methyl-1(9)-octal-2-ones (I) by methylmagnesium iodide in the presence of cuprous salts.[3] The parent compound Ia afforded the *cis*-decalone IIa as the sole 1,4 adduct, whereas the 7α-substituted homologs Ib and Ic gave only the 1,2 adducts IIIb and IIIc.

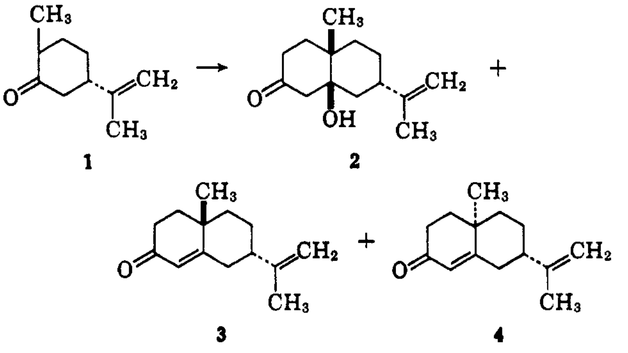


a, R = H
b, R = $CH_2C{=}CH_2$
c, R = $(CH_3)_2CH$

These findings suggested to us that with Ib and Ic, unfavorable interactions between C-1 and the respective C-7 substituent increased the energy of the transition state for 1,4 addition relative to that for the competing 1,2 addition reaction. We now describe some additional studies along these lines which reinforce this viewpoint.

Octalone **4** has an equatorial isopropenyl grouping at C-7 and, according to the aforementioned postulate, would be expected to undergo the 1,4 addition reaction. This octalone was prepared *via* Robinson annelation of (−)-dihydrocarvone and methyl vinyl ketone.[3] As previously noted,[3,4] this reaction affords principally the crystalline ketol **2** with *trans*-oriented methyl and isopropenyl groups. However, the material remaining after collection of the crystalline product contained a fair amount of octalone **4** and, presumably, its ketol and dione precursors. Treatment of this residue with refluxing aqueous base led to a mixture of the isomeric octalones **3** and **4** with the former predominating 2.5 to 1. The latter isomer was obtained *via* fractional crystallization of the semicarbazone derivatives followed by preparative gas chromatography and column elution chromatography of the ketonic mixture regenerated from the enriched semicarbazone fractions.

Having previously found that octalone **3** gives no conjugate methylation products with the cupric acetate–methylmagnesium iodide reagent of Birch and Smith,[5] we felt that we could carry out our present studies on mixtures of octalones **3** and **4** with the expectation of obtaining 1,4 adducts related only to **4**.



This was indeed the case. Decalone **5** could be isolated in 16–21% yield, based on octalone **4**, from such addition reactions. The by-products of these reactions consisted largely of the expected tertiary alcohols which were readily separated from decalone **5** by column chromatography. Lithium dimethylcopper, a reagent recently employed by House and coworkers[6] for similar 1,4 additions, afforded decalone **5** in 40% yield. In this case, a substantial portion of the octalone **3** initially present was recovered unchanged and a small amount of what appears to be the 1,4 adduct of octalone **3** was detected by gas chromatography. The recovery of ketonic materials is concordant with the results of House, *et al.*,[6] who found that lithium dimethylcopper adds only slowly to ketonic carbonyl groups.

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[1] Fellow of the Alfred P. Sloan Foundation, 1966–1968.

[2] National Institutes of Health Predoctoral Fellow, Institute of General Medical Sciences, 1965–1968.

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