Chemistry of α-Haloaldehydes. III.[1] Reaction of 2-Halo-2-methylpropanal with Malonic Esters in the Presence of Potassium Carbonate (Synthesis of γ-Butyrolactones)

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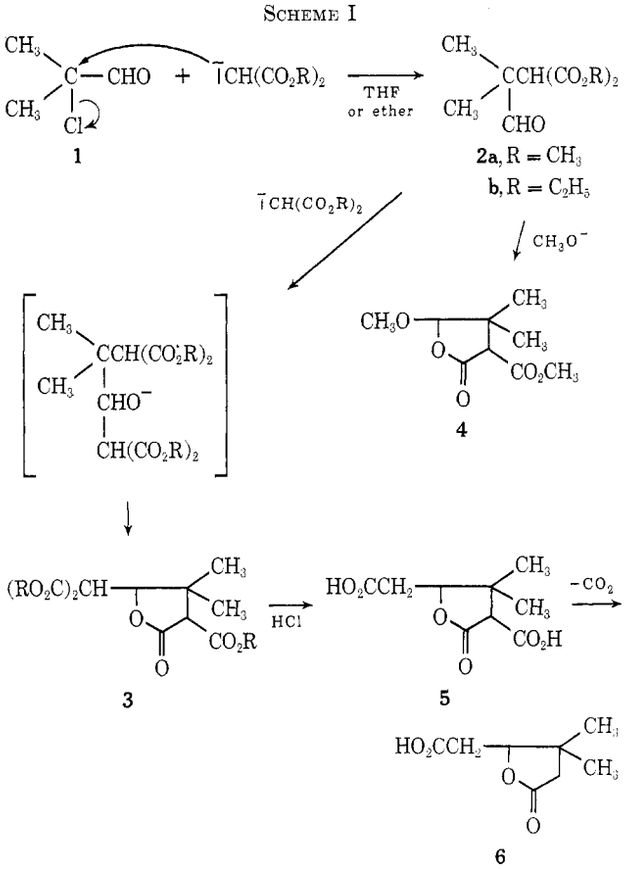
A new method for the preparation of γ-butyrolactone has been described. The reaction of 2-chloro-2-methylpropanal (1) with dimethyl malonate in the presence of potassium carbonate carried out under mild conditions gave γ-butyrolactone derivatives in good yields. The reaction of 1 with dimethyl malonate in tetrahydrofuran (THF) affords a mixture of methyl 3-formyl-2-methoxycarbonyl-3-methylbutanoate (**2a**) and α-methoxycarbonyl-β,β-dimethyl-γ-dimethoxycarbonylmethyl-γ-butyrolactone (**3**). The yield of the lactone **3** was greatly improved when 2 equiv of dimethyl malonate in THF was used. Treatment of **2a** with sodium methoxide gave α-methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (**4**). Aldehyde **2a** further reacted with dimethyl sodiomalonate giving the lactone **3**. Aldehyde 1 reacted with 2 equiv of dimethyl malonate in aqueous potassium carbonate to give predominantly α-methoxycarbonyl-β-dimethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (**10**). The hydrolysis of the lactone 10 with concentrated HCl gave α-carboxy-β-carboxymethyl-γ,γ-dimethyl-γ-butyrolactone (**11**), which was decarboxylated to *dl*-terpenylic acid (**12**) by heating.

In previous papers[1,2] we reported the base-catalyzed condensation of α-haloaldehydes with dichloro- and monochloroacetates to afford corresponding haloepoxyalkanoates. The present paper describes the result of the title reaction attempted for the synthesis of γ-butyrolactone derivatives as is exemplified by the reaction of 2-chloro-2-methylpropanal (**1**) which was carried out under various conditions using potassium carbonate as a catalyst.

When the reaction was conducted at room temperature in tetrahydrofuran (THF) using 1 equiv each of dimethyl malonate and the aldehyde **1**, methyl 3-formyl-2-methoxycarbonyl-3-methylbutanoate (**2a**) was obtained in a 60% yield together with α-methoxycarbonyl-β,β-dimethyl-γ-dimethoxycarbonylmethyl-γ-butyrolactone (**3**, 26%). The lactone **3** has been confirmed to be derived by the subsequent reaction of **2a** with dimethyl malonate by a separate experiment. Thus the yield of the lactone **3** was significantly improved when 2 equiv of malonate in THF were used. On the other hand, the reaction of the formylbutanoate **2a** with methoxide ion similarly resulted in an intramolecular cyclization to afford α-methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (**4**) in a 65% yield. The analogous reaction of **1** with dimethyl malonate in ether afforded the methoxylactone **4** (20% yield) and the lactone **3** (46% yield). The reaction sequence for the formation of the lactones **3**, and **4** is shown in Scheme I. The structural assignment of these products was made on the basis of ir and nmr data. Ir absorptions of **3** at 1790, 1760, and 1728 cm^{-1} indicate the presence of γ-butyrolactone ring and two ester groups, respectively. The lactone ring skeleton is also supported by the nmr spectrum taken in $CDCl_3$, which exhibited a singlet at δ 3.28 ppm (α-methine proton) and two doublets at δ 5.04 and 3.67 ppm (1 H each, J = 10.5 Hz, γ-methine proton and δ-methine proton). The structure of **2a** was determined by nmr and mass spectrum [m/e 174 (M^+ − CO) and 171 (M^+ − OCH_3)]. Although the nmr signal of **2a** observed at 3.74 ppm as a singlet apparently is due to its methine proton, it was hardly distinguishable from the very close-lying singlet at 3.72 ppm due to two ester methyl protons. On the contrary, the nmr spectrum of ethyl 2-ethoxycarbonyl-3-methyl-3-formylbutanoate (**2b**) measured in $CDCl_3$ showed a sharp singlet at δ 3.60 ppm (methine proton) and the ethyl ester patterns at δ 1.26 and 4.17 ppm.

SCHEME I



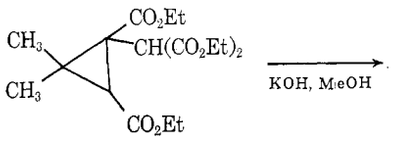
The ester cleavage[3] of the lactone **3** to α-carboxy-β,β-dimethyl-γ-carboxymethyl-γ-butyrolactone (**5**) was effected in a 97% yield by heating with concentrated hydrochloric acid at 70–80° for 24 hr. The nmr spectrum of the lactone acid **5** in trifluoroacetic acid showed four singlets at δ 1.13, 1.30, 1.32, and 1.45 ppm due to β,β-dimethyl protons and two singlets at δ 3.63

(1) Preceding paper: A. Takeda, S. Tsuboi, and T. Hongo, *Bull. Chem. Soc. Jap.*, **46**, 1844 (1973).

(2) A. Takeda, S. Tsuboi, S. Wada, and H. Kato, *Bull. Chem. Soc. Jap.*, **45**, 1217 (1972).

(3) Neither alkaline hydrolysis nor heating with 20% H_2SO_4 was effective.

and 3.83 ppm due to α-methine proton. This rather complicated pattern indicates that the product consists of a diastereomeric mixture. This estimation is compatible with the fact that the lactone acid **5** was decarboxylated to a uniform product, β,β-dimethyl-γ-carboxymethyl-γ-butyrolactone (**6**), mp 89.5–90°. The nmr spectrum of **6** in trifluoroacetic acid showed a clear pattern involving two singlets at δ 1.22 and 1.37 ppm due to two methyl protons, a singlet at δ 2.73 ppm due to α-methylene protons, a doublet (J = 7 Hz) at δ 2.93 ppm due to branched methylene protons, and a triplet (J = 7 Hz) at δ 4.98 ppm due to γ-methine proton. In 1901, Perkin and Thorpe reported the synthesis of the lactone **6** with the mp 154–156°.[4] They noted that the hydrolysis of diethyl (1,3-diethoxycarbonyl-2,2-dimethylcyclopropyl)malonate (**7**) with boiling methanolic potassium hydroxide afforded β,β-dimethyl-γ-carboxy-γ-carboxymethyl-γ-butyrolactone (**8**) which was then decarboxylated to the compound **6**.



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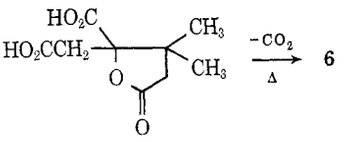

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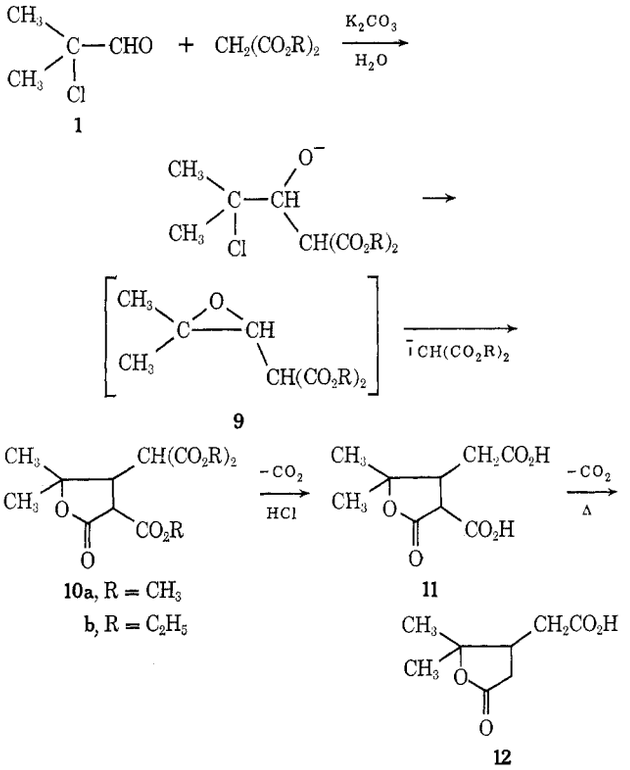
In order to solve the question about the discrepancy of melting points we reexamined their experiment. Both spectral data and analysis did not support such structures as they reported. The results of the reinvestigation of Perkin's experiment on the synthesis of compound **6** will be published elsewhere.[4]

The reaction of **1** with malonic esters conducted in aqueous potassium carbonate proceeded in different ways. It gave α-alkoxycarbonyl-β-dialkoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (**10**) in good yields (70–82%). The formation of the lactone **10** may be well explained by assuming the intermediate **9**, which further reacted with malonate as is shown in Scheme II. The reaction carried out in dry methanol gave a mixture of lactone **4** (22% yield) and **10a** (17% yield).

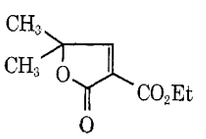
The hydrolysis of the lactone **10** with concentrated hydrochloric acid gave the free acid **11** in a 98% yield. When heated at 172–180°, compound **11** was transformed to terpenylic acid (**12**)[5] quantitatively, with the loss of carboxyl group attached to the α carbon. Terpenylic acid is usually prepared by the oxidation of α-terpineol. The yield is not satisfactory, however, because of the formation of several by-products. Accordingly, the route by way of compound **11** described here provides us with a convenient procedure for the synthesis of terpenylic acid. It has been reported by Franke and Groeger[6] that 2-bromo-2-methylpropanal reacted with diethyl sodiomalonate in ethanol to

(4) W. H. Perkin and J. F. Thorpe, *J. Chem. Soc.*, **79**, 763 (1901).
(5) C. Hempel, *Justus Liebigs Ann. Chem.*, **180**, 79 (1875). Compound **12** isolated by us melts at 88–89° (lit. mp 89–90°).
(6) A. Franke and G. Groeger, *Monatsh. Chem.*, **43**, 55 (1922).

SCHEME II



give α-ethoxycarbonyl-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-γ-butenolide (**13**). In reinvestigating their experiment, we followed



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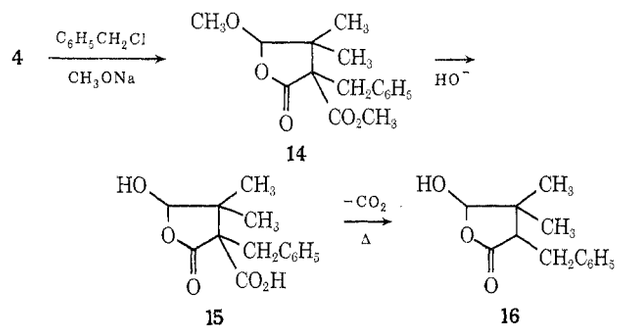
the procedure literally, but we failed to isolate the butenolide **13** and obtained only the lactone **10b** in a 53% yield. Therefore, there remains some doubt as to the actual isolation of the compound **13** as reported by Franke, *et al.* The structure of **10** was determined by analysis and spectral data. The ir band of **10a** at 1760 cm^{-1} is characteristic of γ-butyrolactone. The nmr spectrum in $CDCl_3$ showed two singlets at δ 1.33 and 1.52 ppm due to methyl protons, three singlets at δ 3.69, 3.75, and 3.78 ppm due to three methyl ester protons, and a multiplet at δ 3.25–4.0 ppm due to α-, β-, and branched methine protons, while no signals appeared at around 5.04 ppm indicating the absence of γ-methine proton. The nmr spectrum of **11** in trifluoroacetic acid showed unambiguous patterns. Two methine protons of the lactone ring appeared at δ 3.37 ppm (dd, 1 H, J = 6 and 11 Hz) and δ 4.01 ppm (d, 1 H, J = 11 Hz), respectively. The geometry of **11** is deduced to be trans from the large coupling constant ($J_{\alpha,\beta}$ = 11 Hz).

To obtain a firm support for the structures and also to study the reactivity of their α carbon, we carried out the reaction of the lactones **3**, **4**, and **10** with benzyl chloride in the presence of sodium methoxide. While the lactones **3** and **10** were recovered unreacted, the methoxylactone **4** gave α-benzyl-α-methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (**14**) in a 28% yield. The nmr spectrum of **14** in CCl_4 showed a

singlet at δ 7.09 ppm due to phenyl protons and no signals at around δ 3.53 ppm due to the α-methine proton. Hydrolysis of the benzyllactone **14** with methanolic sodium hydroxide gave hydroxylactone **16** (50% yield) and lactone acid **15** (42% yield). On heating at 180°, **15** underwent decarboxylation to afford **16** in a quantitative yield. In nmr spectrum of **15** and **16**, resonances of the γ proton appeared at δ 5.60 and 5.18 ppm, respectively. The reaction sequence for the formation of the lactones **14**, **15**, and **16** is shown in Scheme III. These unusually high δ values

SCHEME III



are attributable to the deshielding effects of the hydroxyl group and the lactone ring oxygen. The signals of β-methyl protons in **16** appear upfield (0.86–1.01 ppm) from those of **4**, as a result of the shielding effect of the phenyl group.

On the whole, it might be concluded that in aprotic solvents such as THF the carbanion of malonic esters becomes more nucleophilic than in protic solvent so that it attacks the α carbon of the α-haloaldehyde, thus forming C–C bond by SN reaction followed by an intramolecular cyclization to afford γ-lactones **3** and **4**, whereas, in protic solvents such as H_2O, the carbanion attacks the carbonyl carbon polarized by solvent molecule forming C–C bond by nucleophilic addition followed by an intramolecular cyclization to afford γ-lactone **10**.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano. Analytical determinations by glpc were performed on a Hitachi K-53 model gas chromatograph (3 mm o.d. × 1 m, 10% Apiezon Grease L on Chromosorb W). The mass spectra were obtained with a Hitachi RMS-4 mass spectrometer (70 eV). We are indebted to Mr. Hiroshi Ooyama, Hokko Chemical Industry Co., Ltd., and Mr. Heizan Kawamoto and Miss Hiromi Ootani for the nmr measurements (60 MHz).

2-Chloro-2-methylpropanal (**1**) was prepared by the method of Stevens[7] by treating aldehydes with sulfuryl chloride, bp 86–90° (lit.[7] bp 86–88°), yield 86%. 2-Bromo-2-methylpropanal was prepared by brominating 2-methylpropanal in the presence of calcium carbonate in ether, bp 105–112° [lit.[8] bp 48° (8 mm), lit.[9] bp 112–113°], yield 43%.

Methyl 3-Formyl-2-methoxycarbonyl-3-methylbutanoate (2a).—To a solution of 22.3 g (0.17 mol) of dimethyl malonate in 100 ml of dry THF was added 23.4 g (0.17 mol) of potassium carbonate at room temperature. A solution of 18 g (0.17 mol) of **1** in 50 ml of dry THF was then added to the mixture. After being stirred at room temperature for 6 days, the mixture was poured into water. It was acidified with 10% HCl and the organic layer was extracted with ether. The ethereal extract was washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue, on distillation, gave 20.5 g (60%) of **2a**: bp 96–97° (3 mm); ir (neat) 2760 (CHO), 1740 (C=O), 1438, 1340, 1260, 1170, 1050, 902 cm^{-1}; nmr (CCl_4) δ 1.17 (s, 6, 2 CH_3), 3.72 [s, 6, $(CO_2CH_3)_2$], *ca.* 3.74 [s, 1, $CH(CO_2CH_3)_2$], 9.53 (s, 1, CHO); mass spectrum *m/e* (rel intensity) 174 (4, $M^+ - CO$), 171 (6, $M^+ - OCH_3$), 159 (3), 142 (20), 139 (46), 115 (55), 114 (70), 83 (100), 59 (38), 32 (10), 29 (34), 28 (56).

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.50; H, 6.82.

The undistillable material was recrystallized from benzene to give 6.7 g (26%) of **3**.

α-Methoxycarbonyl-β,β-dimethyl-γ-dimethoxycarbonylmethyl-γ-butyrolactone (3) showed mp 120–120.5°; ir (Nujol) 1790 (lactone C=O), 1760, and 1728 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.14 (s, 3, C-β CH_3), 1.21 (s, 3, C-β CH_3), 3.28 (s, 1, C-α H), 3.67 [d, 1, J = 10.5 Hz, $CH(CO_2CH_3)_2$], 3.77 (s, 9, 3 CO_2CH_3), 5.04 (d, 1, J = 10.5 Hz, C-γ H).

Anal. Calcd for $C_{13}H_{18}O_8$: C, 51.66; H, 6.00. Found: C, 52.00; H, 5.94.

Ethyl 3-Formyl-2-ethoxycarbonyl-3-methylbutanoate (2b).—From a mixture of **1** (5 g, 0.047 mol), diethyl malonate (7.5 g, 0.047 mol), potassium carbonate (6.5 g, 0.047 mol), and dry THF (80 ml), 4.7 g (44%) of a liquid distilling at 114–115° (4.5 mm) was obtained by the same treatment as described in the preparation of **2a**: ir (neat) 2760 (CHO), 1740 (C=O), 1478, 1380, 1334, 1255, 1165, 1050, 901 cm^{-1}; nmr (CCl_4) δ 1.19 (s, 6, 2 CH_3), 1.26 (t, 6, J = 7.5 Hz, 2 $CO_2CH_2CH_3$), 3.60 [s, 1, $CH(CO_2C_2H_5)_2$], 4.17 (q, 4, J = 7.5 Hz, 2 $CO_2CH_2CH_3$), 9.5 (s, 1, CHO).

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.30; H, 8.26.

Reaction of 2a with Dimethyl Malonate.—To a solution of 3.8 g (0.029 mol) of dimethyl malonate in 30 ml of dry ether was added 1.6 g (0.029 mol) of sodium methoxide at room temperature. A solution of 5.8 g (0.029 mol) of **2a** in 20 ml of dry ether was added dropwise at 0–5° and the mixture was then stirred for 30 min. After standing overnight at room temperature, the mixture was refluxed for 6 hr. An equivalent amount of water was added to the mixture and then the ethereal layer was separated. When the aqueous layer was acidified with 10% HCl, white crystals precipitated. The solid was collected, thoroughly washed with water, and air dried to give 3.3 g (38%) of white crystals, mp 119–120°. It was identified as **3** by comparison of ir and nmr spectra with those of the authentic sample. The ethereal layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the residual oil was distilled to yield 1.3 g of dimethyl malonate, bp 48–50° (4 mm), and 1.1 g of **2a**, bp 104–105° (3.5 mm).

Reaction of 1 with Two Equivalents of Dimethyl Malonate.—To a solution of 32.2 g (0.244 mol) of dimethyl malonate in 100 ml of dry THF was added 33.8 g (0.244 mol) of potassium carbonate at room temperature. Then a solution of 13 g (0.122 mol) of **1** in 20 ml of dry THF was added to the mixture. After being stirred at room temperature for 3 days, the mixture was poured into a large quantity of water and acidified with 10% HCl. The organic layer was extracted with ether, and then 14.3 g of **3** precipitated. The ethereal layer was washed with water and dried over $MgSO_4$ for 2 hr. After removal of the solvent, the residue, on distillation, gave 12 g of dimethyl malonate and 7 g (28%) of **2a**, bp 96–99° (3 mm). The undistillable material was washed with ether to give 0.9 g (total yield 41%) of white crystals whose ir and nmr spectra were identical with those of an authentic sample of **3**.

α-Methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (4).—To a solution of 1 g (0.005 mol) of **2a** in 30 ml of dry ether was added 0.27 g (0.005 mol) of sodium methoxide at room temperature. After being refluxed for 18 hr, the mixture was cooled and acidified with 5% HCl. The ethereal layer was separated, washed with water, and dried over $MgSO_4$. After removal of the solvent, 0.65 g (65%) of colorless needles was obtained: mp 53–55° (from benzene); ir (Nujol) 1790 (lactone C=O), 1730 (ester C=O), 1435, 1340, 1200, 1110, 960, 740 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (s, 3, β-CH_3), 1.25 (s, 3, β-CH_3), 3.50 (s, 3, OCH_3), 3.53 (s, 1, α-H), 3.76 (s, 3, CO_2CH_3), 4.96 (s, 1, γ-H); mass spectrum *m/e* 201 ($M^+ - 1$), 171 ($M^+ - OCH_3$), 143 ($M^+ - CO_2CH_3$), 139, 127, 115, 114, 111, 95, 83, 82, 75, 73, 71, 67, 55.

(7) C. L. Stevens and B. T. Gillis, *J. Amer. Chem. Soc.*, **79**, 3448 (1957).

(8) T. A. Favorskaya and D. A. Shkurgina, *J. Gen. Chem. USSR*, **25**, 713 (1955); *Chem. Abstr.*, **50**, 2427 (1956).

(9) L. A. Yanovskaya and A. P. Terent'ev, *Zh. Obshch. Khim.*, **22**, 1598 (1952); *Chem. Abstr.*, **47**, 9258 (1953).

Anal. Calcd for $C_9H_{14}O_6$: C, 53.46; H, 6.98. Found: C, 53.37; H, 7.10.

Reaction of 1 with Dimethyl Sodiomalonate in Ether.—Sodium (2.3 g, 0.1 mol) was dissolved in 60 ml of absolute methanol with moderate cooling. To the solution was added 13.2 g (0.1 mol) of dimethyl malonate at 30–40°. Removal of the solvent left 15.4 g (0.1 mol) of dimethyl sodiomalonate. To a solution of 10.6 g (0.1 mol) of **1** in 55 ml of dry ether was added in several portions 15.4 g (0.1 mol) of dimethyl sodiomalonate at −3 to 3° with stirring. The mixture was stirred for 1 hr at 0° and then for 3 hr at room temperature. After standing overnight, it was refluxed for 6 hr. After being cooled, it was poured into a large quantity of water. The organic layer was extracted with ether. The ethereal layer was washed with water and dried over Na_2SO_4. After removal of the solvent the residue, on distillation, gave 4.1 g (20%) of **4**, bp 122–124° (5 mm), mp 53–55° (benzene). Ir and nmr spectra were identical with those of the authentic sample. The aqueous layer was acidified with 1 *N* HCl. The precipitated crystals were collected, washed with water and ether, and air dried to give 6.9 g (46%) of **3**, mp 118–119° (chloroform–ether). Ir and nmr spectra were identical with those of the authentic sample.

α-Carboxy-β,β-dimethyl-γ-carboxymethyl-γ-butyrolactone (5).—A mixed solution of 3.9 g (0.013 mol) of **3** in 20 ml of concentrated HCl was stirred at 70–80° for 24 hr. Removal of concentrated HCl gave 2.7 g (97%) of **5**. An analytical sample was obtained by recrystallization from acetone–ether: mp 146–148°; ir (KBr) 2650 (COOH), 1780 (lactone C=O), 1700 cm^{-1} (acid C=O); nmr (CF_3CO_2H) δ 1.13 (s, β-CH_3), 1.30 (s, β-CH_3), 1.32 (s, β-CH_3) and 1.45 (s, β-CH_3) (cis–trans mixture, 6), 2.88 (d, 2, J = 6.5 Hz, CH_2CO_2H), 3.63 (s, α-H) and 3.83 (s, α-H) (cis–trans mixture, 1), 4.89 (m, 1, γ-H).

Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.03; H, 5.32.

β,β-Dimethyl-γ-carboxymethyl-γ-butyrolactone (6).—Compound **5** (0.14 g, 0.63 mmol) was heated at 180–200° for 30 min. Crude **6** was recrystallized from ether–acetone to give 0.11 g (98%) of pure **6**: mp 89.5–90° (benzene) (lit.[4] mp 154–156°); ir (KBr) 2950, 2650 (CO_2H), 1780 (lactone C=O), 1700 cm^{-1} (acid C=O); nmr (CF_3CO_2H) δ 1.22 (s, 3, cis CH_3), 1.37 (s, 3, trans CH_3), 2.73 (s, 2, α-H), 2.93 (d, 2, J = 7 Hz, CH_2CO_2H), 4.98 (t, 1, J = 7 Hz, γ-H).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.79; H, 6.84.

α-Methoxycarbonyl-β-dimethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (10a).—To a solution of 13.8 g (0.1 mol) of potassium carbonate in 56 ml of water was added 13.2 g (0.1 mol) of dimethyl malonate. Aldehyde **1** (10.7 g, 0.1 mol) was added and the mixture was stirred at room temperature for 30 hr. After addition of ether, the mixture was acidified with 10% HCl. The precipitated crystals were collected, washed with water and ether, and air dried to give 6.9 g of **10a**. The filtrate was extracted with ether and the ethereal layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the residual oil crystallized. The solid was recrystallized from *n*-hexane–benzene (1:1) to give 5.5 g of **10a**. The total yield of **10a** was 82%: mp 87–89°; ir (Nujol) 1760 (lactone C=O), 1738 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.33 (s, 3, γ-CH_3), 1.52 (s, 3, γ-CH_3), 3.69 (s, 3, CO_2CH_3), 3.75 (s, 3, CO_2CH_3), 3.78 (s, 3, CO_2CH_3), 3.25–4.0 [m, 3, γ-H, β-H and $CH(CO_2CH_3)_2$].

Anal. Calcd for $C_{13}H_{18}O_8$: C, 51.66; H, 6.00. Found: C, 51.86; H, 6.11.

α-Ethoxycarbonyl-β-diethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (10b).—A mixture of **1** (61.9 g, 0.58 mol), diethyl malonate (186 g, 1.16 mol), potassium carbonate (161 g, 1.16 mol), and water (250 ml) was stirred at 35–40° for 20 hr. The mixture was acidified with 10% HCl and the organic layer was extracted with ether. The ethereal layer was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue, on distillation, gave 140 g (70%) of **10b**: bp 188–191° (1.2 mm); ir (neat) 1770 (lactone C=O), 1730 cm^{-1} (ester C=O); nmr (CCl_4) δ 1.12–1.42 (m, 9, 3 $CO_2CH_2CH_3$), 1.20 (s, 3, γ-CH_3), 1.42 (s, 3, γ-CH_3), 3.22 (m, 1, β-H), 3.43 (d, 1, J = 11 Hz, α-H), *ca.* 3.65 [d, 1, J = 11 Hz, $CH(CO_2C_2H_5)_2$], 4.03 (m, 6, 3 $CO_2CH_2CH_3$).

Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.02. Found: C, 56.15; H, 7.10.

Reaction of 1 with Dimethyl Malonate in the Presence of Sodium Methoxide in Absolute Methanol.—To a solution of 10.6 g (0.1 mol) of **1** in 30 ml of absolute methanol was added a methanol solution of dimethyl sodiomalonate prepared from absolute methanol (60 ml), sodium (2.3 g, 0.1 mol), and dimethyl malonate (13.2 g, 0.1 mol). After addition was completed, the mixture was stirred for 1 hr at 0° and then for 1.5 hr at room temperature. After being refluxed for 7 hr with stirring, the mixture was filtered to remove the precipitated sodium chloride. After removal of the solvent, the residue was extracted with ether and the ethereal solution was washed with water and dried over Na_2SO_4. Removal of the solvent left a clean oil which on distillation gave 3.9 g (22%) of **4**, bp 128–129° (4 mm), and 2.5 g (17%) of **10a**, bp 160–170° (0.25 mm): mp 87–89° (*n*-hexane–acetone). Each component was identified by comparison of ir and nmr spectra with those of the authentic samples.

α-Carboxy-β-carboxymethyl-γ,γ-dimethyl-γ-butyrolactone (11).

A. From 10a.—A mixed solution of 10 g (0.033 mol) of **10a** in 30 ml of concentrated HCl was stirred at 60° for 13 hr and then at 70–75° for 6 hr. Removal of concentrated HCl gave 7 g (98%) of **11** which, on tlc analysis,[10] showed one clean spot with the R_f value of 0.23: mp 161–163° (acetone); ir (KBr) 2650 (CO_2H), 1765 (lactone C=O), 1715 cm^{-1} (acid C=O); nmr (CF_3CO_2H) δ 1.47 (s, 3, cis CH_3), 1.70 (s, 3, trans CH_3), 2.85 (d, 2, J = 6 Hz, CH_2CO_2H), 3.37 (dd, 1, J = 6 and 11 Hz, β-H), 4.01 (d, 1, J = 11 Hz, α-H).

Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.09; H, 5.77.

B. From 10b.—The mixed solution of 4.2 g (0.012 mol) of **10b** in 20 ml of concentrated HCl was stirred at 70–80° for 24 hr. After removal of concentrated HCl the residue was washed with ether to give 0.8 g (35%) of **11**, mp 161–163° (acetone). Ir (Nujol) and nmr (CF_3CO_2H) spectra were identical with those of the authentic sample prepared from **10a**.

β-Carboxymethyl-γ,γ-dimethyl-γ-butyrolactone (12).—Compound **11** (0.11 g, 0.52 mmol) was heated at 175–180° until evolution of carbon dioxide ceased and 0.089 g (100%) of **12**[11] was obtained: mp 88–89° (acetone–ether) (lit.[5] mp 89–90°); ir (KBr) 3000, 1750 (lactone C=O), 1710 cm^{-1} (acid C=O); nmr (CF_3CO_2H) δ 1.42 (s, 3, cis CH_3), 1.62 (s, 3, trans CH_3), 2.74 (d, 2, J = 12 Hz, CH_2CO_2H), 2.69–3.31 (m, 3, α-H and β-H).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 56.01; H, 7.19.

Reaction of 2-Bromo-2-methylpropanal with Diethyl Sodiomalonate.[6]—Sodium (3.2 g, 0.14 mol) was dissolved in 65 ml of absolute ethanol with moderate cooling. A solution of 48 g (0.3 mol) of diethyl malonate in 10 ml of absolute ethanol was then added dropwise at 20° with stirring. To the resulting solution was added dropwise 13.5 g (0.089 mol) of 2-bromo-2-methylpropanal at room temperature. After stirring was continued for 14 hr at room temperature, the mixture was refluxed for 1 hr. After being cooled, it was poured into 300 ml of water. The mixture was acidified with 10% HCl and the organic layer was extracted with ether. The ethereal solution was washed with water, dried over $MgSO_4$, and evaporated. The residual oil was distilled at 166–170° (0.2 mm) [lit.[6] bp 177–178° (25 mm)] to give 18.2 g (53%) of a clean oil, of which the ir and nmr spectra were identical with those of the authentic sample of **10b**.

α-Benzyl-α-methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (14).—Sodium (0.3 g, 0.013 g-atom) was dissolved in 10 ml of absolute methanol with moderate cooling. To the resulting solution was added 1.5 g (0.0074 mol) of **4** and then 1.9 g (0.015 mol) of benzyl chloride at room temperature with stirring. After stirring was continued for an additional 5 hr at room temperature, the mixture was refluxed for 1 hr. After evaporation of the most of methanol, 100 ml of water was added with cooling. After being acidified with dilute H_2SO_4, the mixture was extracted with ether. The ethereal solution was washed with water and dried over Na_2SO_4. Removal of the solvent gave 0.6 g (28%) of **14**: mp 105–107° (ether); ir (Nujol) 1783 (lactone C=O), 1729 (ester C=O), 1600 cm^{-1} (benzene ring); nmr (CCl_4) δ 1.03 (s, 3, β-CH_3), 1.19 (s, 3, β-CH_3), 3.17 (s, 2, $C_6H_5CH_2$–), 3.52 (s, 3, OCH_3), 3.57 (s, 3, CO_2CH_3), 4.75 (s, 1, γ-H), 7.09 (s, 5, C_6H_5–).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.68; H, 7.06.

α-Benzyl-β,β-dimethyl-γ-hydroxy-γ-butyrolactone (16).—To 5

(10) Condition of tlc: support, silica gel GF_{254} (E. Merck AG, Darmstadt), 0.2 mm; developer, benzene–methanol–acetic acid (10:1:1); spray, Bromocresol Green (B. C. G.).

(11) Tlc analysis showed one spot. Conditions of tlc: support, silica gel GF_{254} (E. Merck AG, Darmstadt), 0.2 mm; developer, benzene–methanol–acetic acid (9:1:1); spray, B. C. G.; R_f value 0.46.

ml of methanol was added 0.22 g (0.0054 mol) of sodium hydroxide dissolved in a small amount of water. To the resulting solution was added 0.8 g (0.0027 mol) of 14 and the mixture was then stirred at 30–40° for 2 days. After being acidified with dilute H_2SO_4, the mixture was extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate and then with water, and dried over Na_2SO_4. Removal of the solvent left 0.5 g of a light yellow oil which, on tlc analysis,[12] showed two spots at the R_f values of 0.36 and 0.58, in a ratio of 3:2. A compound with the R_f value of 0.36 was collected by preparative tlc[13] and identified as **16**: yield 50%; mp 83–84° (ether); ir (Nujol) 3320 (OH), 1760 (lactone C=O), 1598 cm^{-1} (benzene ring); nmr (CCl_4) δ 0.86 (s, 3, cis CH_3 to $C_6H_5CH_2$–), 1.01 (s, 3, trans CH_3 to $C_6H_5CH_2$–), 2.50–3.30 (m, 3, mixture of α-H and benzyl methylene), 4.60 (broad s, 1, OH), 5.18 (s, 1, γ-H), 7.19 (s, 5, $C_6H_5CH_2$–).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.06; H, 7.00.

The aqueous layer was acidified with silute H_2SO_4 to give 0.3 g (42%) of **15**.

α-Benzyl-α-carboxy-β,β-dimethyl-γ-hydroxy-γ-butyrolactone (**15**) showed mp 135–137° (benzene); ir (Nujol) 3400 (OH), 2800–2500 (COOH), 1763 (lactone C=O), 1695 (acid C=O), 1600 cm^{-1} (benzene ring); nmr [$(CD_3)_2CO$] δ 1.22 (s, 6, 2 CH_3), 3.33 (s, 2, $C_6H_5CH_2$–), 5.48 (s, 2, COOH and OH), 5.60 (s, 1, γ-H).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 64.00; H, 6.25.

Registry No.—**1**, 917-93-1; **2a**, 42203-05-4; **2b**, 42203-07-6; **3**, 42203-06-5; **4**, 42203-08-7; *cis*-**5**, 42203-09-8; *trans*-**5**, 42203-10-1; **6**, 42203-11-2; **10a**, 42203-12-3; **10b**, 42203-13-4; **11**, 42203-14-5; **12**, 116-51-8; **14**, 42203-16-7; **15**, 42203-17-8; **16**, 42203-18-9; dimethyl malonate, 108-59-8; diethyl malonate, 105-53-3; dimethyl sodiomalonate, 18424-76-5; diethyl sodiomalonate, 996-82-7; 2-bromo-2-methylpropanal, 13206-46-7.

(12) Conditions of tlc: support, silica gel G (E. Merck AG, Darmstadt), 0.1 mm; developer, *n*-hexane–chloroform–acetone (3:2:1 v/v); spray reagent, H_2SO_4–$KMnO_4$ (7:3 w/w). The spot of **14** on tlc appeared at R_f 0.58.

(13) Conditions of preparative tlc: support, silica gel G (E. Merck AG; Darmstadt), 0.8 mm; developer, *n*-hexane–chloroform–acetone (3:2:1 v/v); eluent, acetone.

Mass Spectrometry in Structural and Stereochemical Problems. CCXXXIV.[1] Alkyl Pyridyl Ketones

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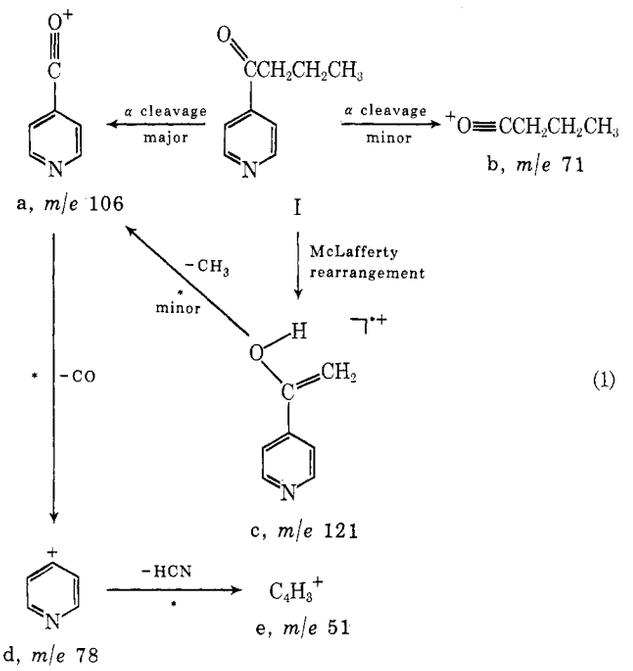
The mass spectra of the three isomeric propyl pyridyl ketones are reported. Negligible influence by the ring nitrogen was observed in the 3 and 4 isomers. Fragmentation of the McLafferty rearrangement ion is observed to occur without prior ketonization. The mass spectrum of propyl 2-pyridyl ketone is markedly different owing to interactions of the side chain with the ring nitrogen. A similar behavior is noted in the higher homologs.

Although the mass spectra of alkyl phenyl ketones have been extensively studied,[2] very little attention has been directed toward the unimolecular decomposition of alkyl pyridyl ketones upon electron impact. This is somewhat surprising in view of much other work on the significant influence of heteroatoms on the fragmentation pattern of many substituted pyridine ions.[3] In light of this and our interest in the electron impact induced fragmentations of ketones,[4] we considered it informative to examine the electron impact induced fragmentations of alkyl pyridyl ketones, specifically the three isomeric propyl pyridyl ketones (I, II, III) and some of their labeled analogs.

Propyl 4-Pyridyl Ketone (I).—The mass spectrum of propyl 4-pyridyl ketone (I) is shown in Figure 1. The major fragmentation pathways are illustrated in eq 1. The elemental composition of the ions was substantiated by high-resolution mass measurements. Its behavior is quite similar to that of butyrophenone with the two major fragmentation pathways being simple cleavage α to the carbonyl group, yielding ions a (*m/e* 106) and b (*m/e* 71) and a McLafferty rearrangement to



(1)

form the ion c of mass 121. Exact mass measurements showed that the expulsion of CO from the molecular ion makes only a 3% contribution to the *m/e* 121 peak. Specific labeling of the three propyl carbons with deuterium also confirms the fragmentation scheme. The McLafferty rearrangement ion c fragments by loss of CH_3 as verified by the observation of the appropriate metastable peak. Examination of the metastable

(1) For the previous paper, see S. Hammerum and C. Djerassi, *J. Amer. Chem. Soc.*, submitted for publication.

(2) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(3) (a) E. V. Brown and M. B. Shambhu, *Org. Mass. Spectrom.*, **6**, 479 (1972); (b) C. S. Barnes, R. J. G. Goldrach, J. Halbert, J. G. Wilson, R. J. Lyall, and S. Middleton, *Tetrahedron Lett.*, 705 (1973); (c) R. G. Cooks, R. N. McDonald, P. T. Cranor, H. E. Petty, and N. L. Wolfe, *J. Org. Chem.*, **38**, 1114 (1973); (d) G. H. Kellen, L. Bauer, and L. L. Bell, *J. Heterocycl. Chem.*, **5**, 647 (1968); (e) R. J. Moser and E. V. Brown, *Org. Mass Spectrom.*, **4**, 555 (1970); (f) C. P. Whittle, *Tetrahedron Lett.*, 3689 (1968); (g) E. V. Brown and R. J. Moser, *J. Heterocycl. Chem.*, **8**, 189 (1971).

(4) K. B. Tomer and C. Djerassi, *Org. Mass Spectrom.*, **6**, 1285 (1972).