of LDA (2.50 mmol) in THF (40 mL) at −78 °C. The reaction mixture was further stirred for 60 min, and water and chloroform were then added. The crude reaction mixture contained compound **2** only as was evident from its TLC, $^1$H NMR, and mass spectra.

**Registry No. 2**, 85135-73-5; **3**, 85135-74-6; **4**, 85135-75-7; 2-cyano-3-hydroxy-3,3-diphenylprop-1-ene, 85135-76-8; acrylonitrile, 107-13-1; benzophenone, 119-61-9; propiolamide, 7341-96-0; cyanoacetylene, 1070-71-9; diisopropylamine, 108-18-9; LDA, 4111-54-0; THF, 109-99-9; DEE, 60-29-7; HMPT, 680-31-9; PME, 110-71-4; DMF, 68-12-2.

## Oxidative Decarboxylation and Decarbonylation of 3,3-Dialkyl-2-oxo Carboxylic Acids and Esters

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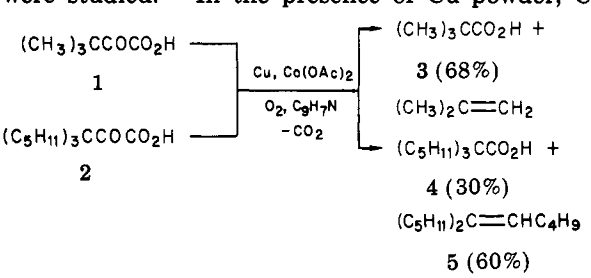
Trialkylacetic acid derivatives have been reported to have muscle-relaxing properties,[1] and many procedures are available for the preparation of the related acids.[2] Alkylation of $\alpha$-metalated $\alpha$-branched acids affords good yields (65–75%) of the trisubstituted acids; however, steric factors may limit the size of the three alkyl groups. The availability of 2-oxo acids and esters [$R_1R_2R_3CCOCO_2H$(R)] in which $R_1$, $R_2$, and $R_3$ are unlike and may have greater than ten carbons suggested that oxidative decarboxylation or decarbonylation of such molecules might offer a procedure for preparing more highly substituted trialkylacetic acids.[3]

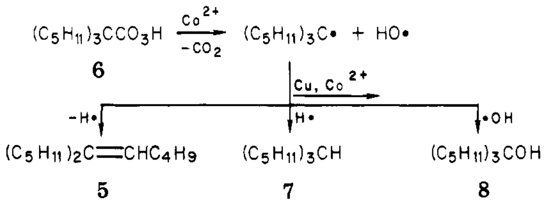
Oxidative decarboxylations of the 2-oxo acids **1** and **2** were studied. In the presence of Cu powder, Co(O-




Ac)$_2$·4H$_2$O, $O_2$, and quinoline, the former was converted to pivalic acid (**3**) in reasonable yields while **2** gave a mixture of tripentylacetic acid (**4**) and 6-pentyl-5-undecene (**5**).

When **1** was heated alone with $CuCO_3 \cdot Cu(OH)_2$ at 130–140 °C, no reaction occurred. In the presence of Cu powder and quinoline, though, **1** was decarboxylated in 77% yield to pivalaldehyde. The addition of oxygen to this system led to 38% of **3**, which was increased to 48% by the introduction of $Co(OAc)_2 \cdot 4H_2O$. The evolution of $CO_2$ varied from 90 to >100%, and qualitative evidence suggested that isobutylene also was formed.

Decarboxylation of **2** did not occur in the presence of Cu powder or a mixture of Cu and $Co(OAc)_2 \cdot 4H_2O$; however, the introduction of $O_2$ to the latter system caused a rapid evolution of $CO_2$. Wieland noticed a similar reaction between pyruvic acid and peroxy disulfate in the presence of palladium.[4] The need for oxygen in the oxidative-decarboxylation reaction suggested the presence of free radicals to account for the formation of the olefin **5**, via loss of carbon dioxide from **4**. However, the latter was found to be stable to the oxidative-decarboxylation conditions. Another possible intermediate in this reaction might have been the peroxy acid **6**, which could have




produced **5**, **7**, and **8**. The autoxidation of aldehydes to peroxy acids is well-known and often is catalyzed by metals such as $Co^{2+}$ or $Mn^{2+}$.[5] Also, the decomposition of peroxy acids, which is catalyzed by metal salts,[6] has produced alcohols, alkanes, alkenes, and other products.[7]

Although the alkane **7** and alcohol **8** were not observed when **2** underwent oxidative decarboxylation in the presence of Cu and $Co^{2+}$, olefin **5** and alcohol **8** resulted when **2** was caused to react with $O_2$ in quinoline solution to which only $Co(OAc)_2$ had been added. The ratio of **5** to **8** changed from 1:2 at 25 °C to 1:7 at 100 °C. Pasky has reported that the decarboxylation of **3** in the presence of $Co(OAc)_2$ and $O_2$ gave, among other products, *tert*-butyl alcohol.[8]

Oxidation of **2** with Cu as the only catalyst afforded **5** plus an unidentified compound. It is conceivable that the presence of Cu in the oxidative decarboxylation inhibited the formation of **8** or caused its rapid dehydration to **5**.

Trimethylpyruvic acid (**1**) was decarboxylated readily to pivalaldehyde by heating with copper powder in quinoline solution. Oxidative decarboxylation with Cu, Co(OAc)$_2$, $O_2$, and quinoline gave pivalic acid in 68% yield.

Attempts to decarbonylate ethyl 3,3-dipentyl-2-oxooctanoate (**9**) catalytically using powdered glass and Fe,

$$\underset{\mathbf{9}}{(C_5H_{11})_3CCOCO_2C_2H_5} \xrightarrow[160\ °C]{KOH,\ TEG} \underset{\mathbf{10}}{(C_5H_{11})_3CCH(OH)CO_2H}\ (94\%)$$

Pd–BaSO$_4$, or $[(C_6H_5)_3P]_3RhCl$ were unsuccessful. The ester **9** was unreactive toward chromic acid, but was converted by alkaline $KMnO_4$ to the keto acid **2**. Alkali at 160 °C in triethylene glycol reduced **9** in 94% yield to the hydroxy acid **10** after acidification. Strong-base reductions of nonenolizable ketones have been carried out previously, as in the preparation of benzhydrol from benzophenone.[9] Two other 2-oxo esters ($R_1R_2R_3CCOCO_2C_2H_5$), where $R_1 = R_2 = R_3 = C_6H_{13}$ and $R_1 = C_4H_9$, $R_2 = C_5H_{11}$, and $R_3 = C_6H_{13}$, were reduced similarly in high yields. The hydroxy acid **10** was treated with periodic acid and was cleaved to

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the corresponding aldehyde in low yield.

## Experimental Section

**Materials.** The 3,3-dialkyl-2-oxo acids and esters were prepared as described previously.[3] Trimethylpyruvic acid was obtained by the permanganate oxidation of pinacolone after the method of Anders.[10]

**Decarboxylation and Oxidative Decarboxylation of 1.** When 12.6 g (0.096 mol) of trimethylpyruvic acid (1) was heated with 0.5 g (0.004 mol) of $CuCO_3{\cdot}Cu(OH)_2$ at 130–140 °C for 10 min, 12 g (95%) of unreacted 1 resulted.

A mixture of 8 g (0.06 mol) of 1, 3.5 g (0.55 mol) of Cu powder, and 50 mL of quinoline then was heated at 175 °C for 1 h, and considerable gas evolution was noted. Distillation of the reaction mixture afforded 4.0 g (77%) of product: bp 66–73 °C; IR (neat) 2710 and 1725 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.09 (s, 9, $(CH_3)_3$), 9.53 (s, 1, CHO); 2,4-dinitrophenylhydrazone mp 209–210 °C (EtOH), lit.[11] for pivalaldehyde 2,4-dinitrophenylhydrazone, mp 210 °C.

Oxygen was passed through a similar reaction mixture at 125 °C for 1 h. It was allowed to cool, poured into dilute HCl, and worked up to give 2.9 g (38%) of pivalic acid (3): bp 163–165 °C, mp 35–36 °C (lit.[12] bp 163–164 °C, mp 35.5 °C).

Cobaltous acetate tetrahydrate (0.3 g, 0.0012 mole) was added to 7.6 g (0.058 mol) of 1, 2.0 g (0.03 mol) of Cu powder, and 50 mL of quinoline, and $O_2$ was passed thru the mixture at 100 °C for 1.25 h. It was worked up as in the previous experiment, and 2.5 g (42%) of 3 resulted. A similar experiment was conducted at 110–120 °C, and the evolved $CO_2$ was collected by passage thru Ascarite. Approximately 96% of the theoretical amount of $CO_2$ was evolved, and 3.75 g (60%) of 3 was isolated.

**Oxidative Decarboxylation of 2.** A mixture of 10 g (0.034 mol) of 3,3-dipentyl-2-oxooctanoic acid (2), 2.5 g (0.04 mol) of Cu powder, 0.4 g (0.0016 mol) of $Co(OAc)_2{\cdot}4H_2O$, and 75 mL of quinoline was heated at 150 °C for 2.5 h, while $O_2$ was passed thru the system. After treatment with dilute HCl, extraction with $Et_2O$, and distillation, two main fractions (4.6 g) were collected. The most abundant (60%), bp 104–105 °C (0.5 mm), had an $^1H$ NMR spectrum and retention time on a SE-30 GC column identical with those of 6-pentyl-5-undecene (5), prepared by the dehydration of tripentylcarbinol.[13] The higher boiling component (30%), bp 145–149 °C (0.5 mm), had infrared and NMR spectra identical with those of a known sample of 2,2-dipentylheptanoic acid (4).[1d]

When 2 was heated with Cu powder and $O_2$ in quinoline solution at 100 °C for 24 h, a mixture resulted that contained 5 and unknown components as shown by GC analysis. However, under comparable conditions except $Co(OAc)_2{\cdot}4H_2O$ was used instead of Cu powder, the reaction product consisted of 73% of 8, 10% of 5, and 17% of 2, as determined by GC. The tripentylcarbinol (8) was isolated by preparative GC, $n^{25}{}_D$ 1.4472 (lit.[13] $n^{20}{}_D$ 1.4470), and identified by comparison of NMR and IR spectra with a known sample.

**Attempts To Decarbonylate 9.** Samples (4 g) of the keto ester 9 were heated at variable temperatures (150–270 °C) with Fe powder and finely ground soft glass, Pd–$BaSO_4$, $[(C_6H_5)_3P]_3RhCl$, $H_2CrO_4$, and alkaline $KMnO_4$. Only in the latter case did a straightforward reaction result, and 70% of 3,3-dipentyl-2-oxooctanoic acid (2) was obtained.

A mixture of 5 g (0.015 mol) of 9 and 50 mL of a hot solution made by mixing 66 g of 85% KOH and 66 g of triethylene glycol was heated at 210 °C for 20 h and then poured into 200 mL of $H_2O$. The organic layer was taken up in ether and acidified with HCl. After ether extraction and concentration, there was obtained 4 g (89%) of a waxy solid: mp 44–45 °C (from nitromethane); $^1H$ NMR $\delta$ 6.9–7.4 (s, 2, COH, $CO_2H$), 4.01 (s, 1, CH), 0.5–1.7 (m, 33, $CH_3$, $CH_2$); IR 3100–3600 (m), 1700 (s) $cm^{-1}$; MS, $m/e$ 301, 302; NE 296. Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 72.07; H, 11.89. When the reaction conditions were changed to 160 °C and 17 h, a 94% yield of 3,3-dipentyl-2-hydroxyoctanoic acid (10) resulted. Under similar conditions, 3,3-dihexyl-2-hydroxynonanoic acid was obtained (93%) from ethyl 3,3-dihexyl-2-oxononanoate: bp 190–194 °C (0.5 mm), mp 27–29 °C. Anal. Calcd for $C_{21}H_{42}O_3$: C, 73.63; H, 12.36. Found: C, 73.87; H, 12.42. 3-Butyl-2-hydroxy-3-pentylnonanoic acid was prepared in a like manner from ethyl 3-butyl-2-oxo-3-pentylnonanoate: bp 190–191 °C (0.15 mm); $n^{25}{}_D$ 1.4610. Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 72.11; H, 12.28.

**Registry No.** 1, 815-17-8; 2, 26269-42-1; 3, 75-98-9; 4, 52061-77-5; 5, 51677-36-2; 8, 5331-63-5; 9, 25594-04-1; 10, 85613-93-0; 3,3-dihexyl-2-hydroxynonanoic acid, 85613-94-1; ethyl 3,3-dihexyl-2-oxononanoate, 85613-95-2; 3-butyl-2-hydroxy-3-pentylnonanoic acid, 85613-96-3; ethyl 3-butyl-2-oxo-3-pentylnonanoate, 25594-03-0; pivaldehyde, 630-19-3; pivaldehyde 2,4-dinitrophenylhydrazone, 13608-36-1.

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# Characterization of Tetrahydroisoquinolines Produced by Pictet–Spengler Reactions of Norepinephrine with Formaldehyde and Acetaldehyde

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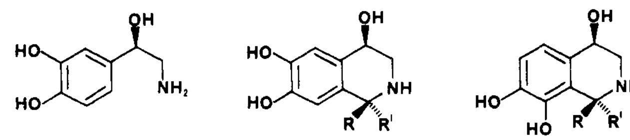
Various symptoms of ethanol intoxication, dependence, and withdrawal may be caused by the reaction of acetaldehyde, the primary metabolite of ethanol, with endogenous catecholamines to produce pharmacologically active tetrahydroisoquinolines.[1] We recently reported that epinephrine (*N*-methyl-1), the major hormone of the adrenal medulla, reacts rapidly with acetaldehyde under physiological conditions to afford a mixture of four isomeric tetrahydroisoquinolinetriols (*N*-methyl-**2b**,**c** and *N*-methyl-**3b**,**c**).[2] In the present investigation we have examined the reaction between acetaldehyde and norepinephrine, the transmitter in most sympathetic postganglionic fibers and certain central nervous system tracts.



1, Norepinephrine 2 3

a, R=R'=H
b, R=$CH_3$, R'=H
c, R=H, R'=$CH_3$

Previous investigations demonstrated that acetaldehyde reacts with norepinephrine in vitro and in tissue samples to afford a product thought to be **2b** or **2c**.[1] However due to its labile nature this material had never been isolated or fully characterized, and an attempt to prepare an authentic sample by an independent synthetic route also failed,[3a] presumably for similar reasons.

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(4) The concentrations of aldehyde and catecholamine in the present study are higher than those employed previously with epinephrine.[2] A comparison of reaction rates must take this into consideration.

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