product of *d*-camphoric anhydride (**10**) in this series we have gained a particularly suitable compound for the separation of terpenes and terpenoids. For instance, a commercial sample of oil of geranium has been readily separated into 31 known and unknown components. Analytical results achieved in resolving complex terpene mixtures will be presented elsewhere.[5]

When used as a liquid chromatographic column phase, compounds **4**, **6**, **9**, and **10** have proved to be perfectly temperature stable over a period of more than a year of constant use, provided that they were "trained" and used at a temperature no higher than 170°. This temperature seems to be the practical limit for this type of columns; raising the temperature by as little as 5° will invariably cause the columns to "bleed," shorten their original retention time, and contaminate the hot wire detector filament to a considerable degree. Thus, properly kept columns have produced matching retention times reproducible in weeks or months within the useful temperature range of 100–170°. In view of a recently presented paper on the subject of retention systems[6] we suggest that this type of column be given some consideration as reference standards, since properly treated columns will not require drift compensation at all.

Experimental

Preparation of N-(3-Hydroxypropyl)phthalimide.—Phthalic anhydride (74 g., 0.5 mole) and 3-aminopropanol (37.5 g., 0.5 mole) were stirred and refluxed with toluene (200 ml). In about 3.5 hr., the theoretical amount of water (9 ml., 0.5 mole) was collected by means of a Dean–Stark phase separator. At this point ice bath cooling of the clear yellow-colored toluene solution caused heavy crystallization. On a Büchner funnel 92.0 g. of light cream-colored solids, m.p. 75–79°, were collected and on concentration the mother liquor afforded an additional 3.8 g. of crystals bringing the yield to 95.4 g. or 93.4%. After three recrystallizations from 80% MeOH, the white crystalline material proved to be gas chromatographically pure, m.p. 78–81°. The infrared spectrum (5% in chloroform) has shown peaks in the λ 2.82, 3.38, *5.62*, *5.83*, *6.08*, *6.20*, 7.12, 7.28, 8.90, 9.28, 10.40, and 10.72 μ areas. The italic peaks are characteristic of the dicarboximide grouping. The n.m.r. spectrum in deuteriochloroform showed a quintet at 1.9 (β-methylene hydrogens), a singlet at 3.00 (hydroxyl hydrogen), and two overlapping triplets centered at 3.65 and 3.84 p.p.m. (α- and γ-methylenes). The aromatic absorption was centered at 7.75 p.p.m. The relative areas of these peaks were 2:1:4:4. Both the infrared spectrum and the n.m.r. data are consistent with formula **2** assigned to this compound.

General Method of Preparation of the Substrates.—An equimolar mixture of the reagents (anhydride and amino glycol) is stirred and refluxed in the presence of an equal volume of toluene. A Dean–Stark phase separator will indicate when the theoretical amount of water has separated. At this point toluene is evaporated *in vacuo*. The remaining buff-colored viscous residue may then be used directly for coating of column supports. Molecular weight determinations, by the melting point depression of camphor solutions according to Rast,[7] have not indicated significant differences from the calculated figures. For some of the compounds the following results were obtained (compound: mol. wt. calcd., found): **4**: 235, 208; **6**: 249, 222; **9**: 255, 252; **10**: 283, 268.

Infrared Spectra.—Solutions (5% in $CHCl_3$) of compounds **4**, **6**, **9**, and **10** have shown characteristic absorption in the λ 2.77–2.95 (OH), 5.62, 5.82, 6.00–6.08 (CO–N–CO), and 9.33–9.60 μ (OH) areas in agreement with the formulas assigned to them. There is good reason to believe that tertiary imides as indicated in formulas **4**, **6**, **9**, and **10** are the major components.[8] At any rate, if condensation polymers were also present as contaminants, they would be of the linear and not of the cross-linked variety since the compounds are clearly soluble in an appropriate solvent (*i.e.*, chloroform).

Polarity of N-[2-(2-Ethyl-1,3-dihydroxy)propyl]-D-camphorimide.—For comparison of polarities two 5 ft. × 1/8 in. o.d. columns were prepared; in both columns −80 to +100 mesh Chromosorb P served as a solid support.

n-Hexyl alcohol, *n*-heptaldehyde, and *n*-hexyl chloride were analyzed in both columns under identical conditions (10%, 100°, 20 cc./min. He flow rate) giving the following retention times on Carbowax 20M: 7.34, 3.2, and 1.76 min.; on **10**: 5.36, 2.48, and 1.52 min. Analyzing the straight-chain saturated hydrocarbons C_{12}, C_{10}, C_8, and C_6 on both columns, under above identical conditions, the following retention times were found on Carbowax 20M: 5.5, 1.7, 0.6, and 0.36 min.; and on **10**: 6.8, 1.96, 0.66, and 0.4 min. The retention indices[6] at 100°, I_{100}, for *n*-hexyl chloride, *n*-heptaldehyde, and *n*-hexyl alcohol on Carbowax 20M are: 1006, 1108, and 1249; on **10** they are: 954, 1049, and 1162. Thus **10** is a comparable though somewhat less polar substrate than Carbowax 20M; on the other hand, it retains hydrocarbons longer than the latter. This is understandable since a monoterpenoid structure represents the nonpolar moiety of this particular hybrid molecule.

Acknowledgment.—We are grateful to Miss Helen Kroboth for her dexterity in preparing the gas chromatographic columns and to the management of the Stepan Chemical Company for permission to publish these results.

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Synthesis of Analogs of δ-Aminolevulinic Acid*[1]

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We have reported earlier on efforts to prepare certain sulfur analogs[3] of the key intermediate in porphyrin biosynthesis, δ-aminolevulinic acid (δ-ALA).[4] We wish now to report on the synthesis of a number of methylated analogs of δ-ALA synthesized by procedures patterned after the successful synthesis of δ-aminolevulinic acid.[5] These compounds will be evaluated for their effect on the biosynthesis of porphyrins.

Discussion

The necessary methyl hydrogen methylsuccinates for the synthetic pathway outlined in Scheme I were pre-

* To Professor Louis F. Fieser.
(1) Supported by U. S. Public Health Service Grants No. CA-02714 and CA-05295.
(2) Abstracted from the Ph.D. Dissertation of T. Padmanathan, University of Pennsylvania, 1963.
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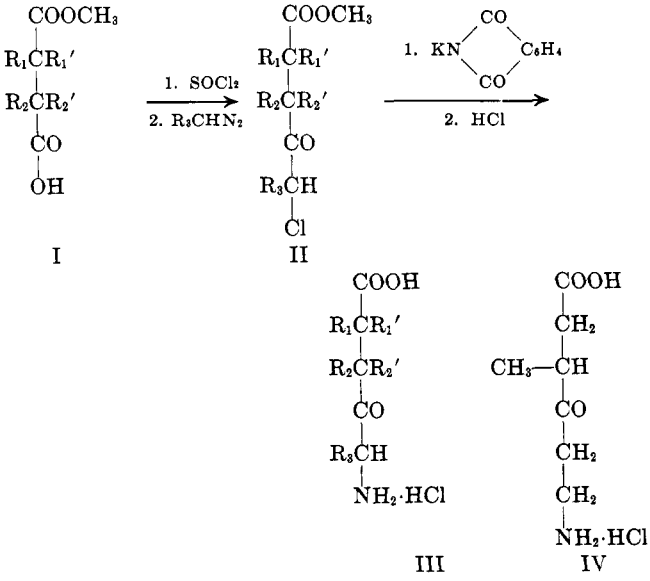
SCHEME I



A, $R_1 = CH_3$; B, $R_2 = CH_3$; C, $R_3 = CH_3$; D, $R_1 = R_1' = CH_3$; E, $R_2 = R_2' = CH_3$; F, $R_2 = R_3 = CH_3$

pared by known procedures and gave no difficulties.[6-10]

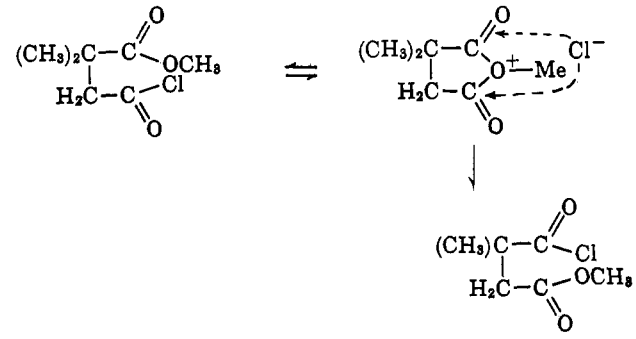
In the dimethyl series, α,α- and β,β-dimethyl δ-ALA (IIID and IIIE) were prepared from a single monoester (ID).[11,12] The acid chloride was shown to undergo partial rearrangement during distillation, giving rise to a mixture of the two possible isomers, which were not separated. Two *p*-nitroanilides, m.p. 107–109° and m.p. 161°, were separated and characterized.

On treatment with diazomethane the acid chloride mixture gave a sharply boiling mixture of the two δ-chlorolevulinates, IID and IIE, which in turn gave rise to a mixture of the two phthalimido derivatives in almost equal proportions. They were easily separated.

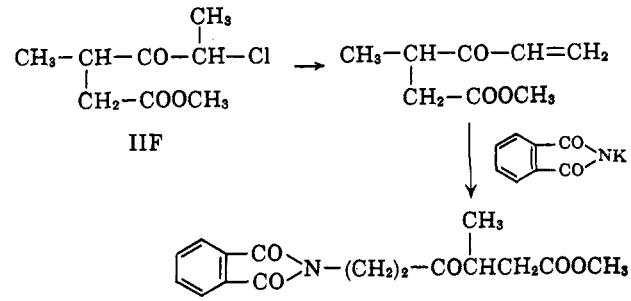
No rearrangement was observed when the experiment was repeated without distilling the acid chloride. Only one anilide (m.p. 161°) and one phthalimido derivative (m.p. 127°) were obtained as products. As would be expected, the primary carbomethoxy group of β,β-dimethylphthalimidolevulinate hydrolyzed faster than the tertiary carbomethoxy group of the α,α-dimethyl derivative. The ester–acid chloride rearrangement undoubtedly proceeds through an oxonium intermediate similar to that proposed earlier for analogous rearrangements of the α,α-diethylglutarate analog,[13] except that the succinate rearrangement apparently can proceed readily without the presence of a Lewis acid catalyst (Scheme II).

The attempted preparation of β,δ-dimethyl-δ-aminolevulinic acid led to the isolation of isomeric 6-amino-3-methyl-4-oxohexanoic acid (IV) and a noncrystalline material which, from n.m.r. data, may have been a mixture of the diastereoisomers of the desired δ-ALA analogs. The isomerization leading to IV probably takes place *via* an elimination[14] and then addition mechanism (Scheme III). Evidently the presence of the additional methyl group in the β-position of the chlorolevulinate IIF, compared to IIC, provides sufficient steric hindrance to SN2 substitution to favor the elimination–addition reaction. No such elimination–addition product was detected during the synthesis of the monomethyl analog, δ-methyl-δ-aminolevulinic acid.

SCHEME II



SCHEME III



Preliminary evidence indicates that some of these analogs of δ-ALA are competitive antagonists for the enzyme system converting two molecules of δ-ALA to the pyrrole, porphobilinogen. This work will be reported elsewhere by Dr. A. S. Stein.

Experimental

α-, β-, and δ-Methyl-δ-aminolevulinic Acids.—The proper carbomethoxypropionyl chloride was treated with diazomethane[15] or diazoethane[16] in ether at −10°, then with dry hydrogen chloride. The chloro ester could be hydrolyzed readily to the chloro acid by aqueous hydrochloric acid at room temperature.

The reaction of the chloro ketone with potassium phthalimide was done in DMF at 80–100°. Ester hydrolysis was accomplished by hot hydrochloric acid in a few minutes, removal of the phthamido residue by refluxing for 6–12 hr.

The structure of the δ-methyl-δ-phthalimidolevulinic acid was confirmed by its n.m.r. spectrum which showed a doublet at τ 8.42 (J = 7.2 c.p.s., intensity 3 protons) as expected for the CH_3CH group, a quadruplet at τ 5.25 (J = 7.2 c.p.s.) corresponding to the CH group, and a single peak at τ 6.8 corresponding to the four methylene hydrogens.

The results and properties are summarized in Tables I, II, and III.

α-Methyl hydrogen α,α-dimethylsuccinate was prepared in 49% yield by the partial hydrolysis of dimethyl α,α-dimethylsuccinate, according to the method of Warren and Weedon,[11] m.p. 42° (lit. m.p. 37–41°,[11] 40.5–41.5°[12]).

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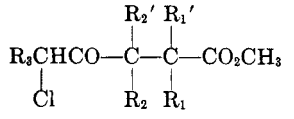
TABLE I

METHYL δ-CHLOROLEVULINATES

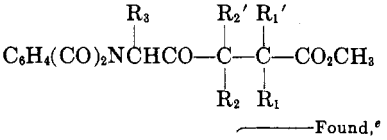


Structure[a]	Yield, %	B.p., °C. (mm.)	n_D (°C.)	Found,[e] % C	H	Cl
$R_1 = CH_3$[b]	91.5	72 (0.2)	1.4530 (24)	47.39	6.14	20.19
$R_2 = CH_3$[c]	85	79 (0.5)	1.4500 (23)	47.19	6.24	20.18
$R_3 = CH_3$[d]	58	64 (0.2)	1.4470 (23)	47.09	6.19	20.04

[a] All other R = H. [b] The free acid: m.p. 74°. *Anal.* Calcd. for $C_6H_9ClO_3$: C, 43.78; H, 5.51; Cl, 21.55. Found: C, 43.84; H, 5.55; Cl, 21.50. [c] The free acid: m.p. 49–51°. *Anal.* Found: 43.92; H, 5.32; Cl, 21.51. [d] The free acid: m.p. 48–49°. *Anal.* Found: C, 43.61; H, 5.64; Cl, 21.79. [e] *Anal.* Calcd.: C, 47.08; H, 6.21; Cl, 19.85.

TABLE II

METHYL δ-PHTHALIMIDOLEVULINATES

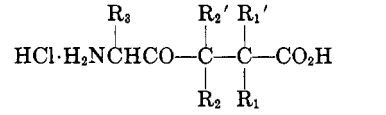


Structure[a]	Yield, %	M.p., °C.	Found,[e] % C	H	N
$R_1 = CH_3$[b]	50	114	62.51	5.53	4.74
$R_2 = CH_3$[c]	54	99	62.14	5.17	4.84
$R_3 = CH_3$[d]	Oil (not purified)				

[a] All other R = H. [b] The free acid: m.p. 183°. *Anal.* Calcd. for $C_{14}H_{13}NO_5$: C, 61.07; H, 4.76; N, 5.09. Found: C, 60.75; H, 5.02; N, 4.97. [c] The free acid: m.p. 146–148°. *Anal.* Found: C, 61.24; H, 4.80; N, 5.33. [d] The free acid: m.p. 108–110°. *Anal.* Found: C, 61.26; H, 4.52; N, 5.24. [e] *Anal.* Calcd.: C, 62.29; H, 5.27; N, 4.84.

TABLE III

δ-AMINOLEVULINIC ACID HYDROCHLORIDES



Structure[a]	Yield, %	M.p., °C. dec.	Found,[e] % C	H	Cl	N
$R_1 = CH_3$[b]	82	138–140	39.93	6.53	19.63	7.80
$R_2 = CH_3$[c]	91	169–170	39.72	6.77	19.55	7.82
$R_3 = CH_3$[d]	96	140–142	39.57	6.51	19.39	7.89

[a] All other R = H. [b] Methyl ester: m.p. 89°. *Anal.* Calcd. for $C_7H_{14}ClNO_3$: C, 42.96; H, 7.21; Cl, 18.12; N, 6.99. Found: C, 42.77; H, 7.31; Cl, 17.90; N, 6.95. [c] Methyl ester: m.p. 108°. *Anal.* Found: C, 42.91; H, 6.99; Cl, 18.01; N, 7.01. [d] Methyl ester: m.p. 110°. *Anal.* Found: C, 42.85; H, 7.14; Cl, 18.21; N, 7.05. [e] *Anal.* Calcd.: C, 39.68; H, 6.66; Cl, 19.53; N, 7.70.

The above monoester–acid (28 g., 0.175 mole), thionyl chloride (35 ml.), and 30 ml. of ether were stirred at room temperature for 24 hr., kept aside for a day, and gently refluxed on a steam bath for 30 min. Excess thionyl chloride and ether were evaporated under reduced pressure. The product, 27.6 g. (88.3%), distilled at 92–94° (20 mm.), $n^{28}D$ 1.4390, $d^{27.5}$ 1.1329.

Anal. Calcd. for $C_7H_{11}ClO_3$: C, 47.08; H, 6.21; Cl, 19.85. Found: C, 47.29; H, 6.24; Cl, 19.66.

The product, a mixture of the two possible isomers, gave a mixture of two ***p*-nitroanilides** when 0.5 g. (0.0028 mole) was added to a well-stirred solution of 0.77 g. (0.056 mole) of *p*-nitroaniline in 30 ml. of benzene. The contents were stirred overnight at room temperature and then refluxed on a steam bath for 30 min. The reaction mixture was cooled and the precipitate (0.60 g.) was collected. The benzene solution gave a viscous residue which crystallized as pale yellow crystals (0.35 g.) from aqueous methanol. After two recrystallizations from the same solvent system with decolorizing charcoal, almost colorless needles were obtained, m.p. 107–109°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 56.84; H, 5.76; N, 9.99. Found: C, 56.61; H, 5.84; N, 9.79.

The benzene-insoluble precipitate was a mixture of *p*-nitroaniline hydrochloride and the isomeric *p*-nitroanilide. The precipitate was successively shaken with water, dilute hydrochloric acid, and water and recrystallized from aqueous methanol. The anilide was obtained as almost colorless needles, m.p. 161°.

Anal. Found: C, 56.83; H, 5.91; N, 9.75.

Methyl α,α- and β,β-Dimethyl-δ-chlorolevulinates.—A well-cooled (−10°) solution of diazomethane (0.25 mole) was treated with the mixture of acid chlorides during 45 min. The mixture was stirred for 45 min., allowed to warm to room temperature (overnight), cooled, and treated with hydrogen chloride for 2.5 hr. A colorless oil (18.2 g., 84.4%) boiling at 60–62° (0.2 mm.) was obtained, $n^{29}D$ 1.4525, d^{28} 1.1469.

Anal. Calcd. for $C_8H_{13}ClO_3$: C, 49.90; H, 6.77; Cl, 18.41. Found: C, 49.95; H, 6.79; Cl, 18.27.

Vapor phase chromatography of a sample on a 20% Carbowax on Chromosorb P column showed two peaks of almost equal intensity.

Methyl α,α- and β,β-Dimethyl-δ-phthalimidolevulinates.—A solution of the above product (10 g., 0.052 mole) in 10 ml. of dimethylformamide was treated with a mixture of potassium phthalimide (9.7 g., 0.052 mole) in 50 ml. of dimethylformamide. Stirring was continued for 1 hr. at room temperature, then for 5 hr. at 100°, followed by overnight at room temperature. The reaction mixture was poured into water, extracted with chloroform, and evaporated to give a semisolid residue. On cooling a chloroform–petroleum ether (b.p. 30–60°) solution of the residue, crystals separated. This material, 4.7 g., m.p. 123–125°, was recrystallized once from chloroform–petroleum ether and then from methanol–water to yield 30% of methyl α,α-dimethyl-δ-phthalimidolevulinate as white plates, m.p. 126–127°.

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.37; H, 5.65; N, 4.62. Found: C, 63.40; H, 5.67; N, 4.60.

The mother liquor from the above product was evaporated to dryness, and the oily residue left behind was shaken with water. Solid melting at 70–75° (4.8 g.) was obtained. It was recrystallized from benzene–petroleum ether (30–60°) to yield 30% of methyl β,β-dimethyl-δ-phthalimidolevulinate as needles, m.p. 80°.

Anal. Found: C, 63.43; H, 5.73; N, 4.78.

β-Carbomethoxyisovaleryl Chloride.—α-Methyl hydrogen α,α-dimethylsuccinate (17.0 g., 0.016 mole), 20 ml. of pure thionyl chloride, and 20 ml. of ether were stirred for 24 hr. at room temperature without heating. Excess thionyl chloride and ether were removed under a stream of nitrogen at 35 mm. pressure, followed by 4 hr. at 20-mm. pressure. The product (18.95 g.) obtained was not distilled.

When the above acid chloride was treated with *p*-nitroaniline in dioxane solution at room temperature, the anilide melting at 161° was obtained as the only product in 79.7% yield.

Methyl α,α-Dimethyl-α-phthalimidolevulinate.—The above undistilled acid chloride (16.0 g., 0.0899 mole) was treated with excess diazomethane at −10°. This was followed by standing at room temperature overnight and passage of hydrogen chloride for 2 hr. at −10°. The product was worked up as usual. Evaporation of the solvent from the dried ($MgSO_4$) ether solution under reduced pressure at 30° gave methyl α,α-dimethyl-δ-chlorolevulinate as a yellow oil (16 g.). It was dried under vacuum (0.1 mm.) for 6 hr. (room temperature) and used without distillation in the following conversion.

To a mixture of potassium phthalimide (9.5 g., 0.051 mole) in 50 ml. of dimethylformamide was added the above chloro keto ester (9.5 g.) in 10 ml. of dimethylformamide. Stirring was continued for an hour at room temperature, followed by 12 hr. at 80–100°, and finally 12 hr. at room temperature. Only one product, methyl α,α-dimethyl-δ-phthalimidolevulinate (9.0 g., 58%), m.p. 126–127°, was obtained.

When the acid chloride was prepared at room temperature, but distilled twice to yield liquid boiling at 91–93° (20 mm.), it gave a mixture of methyl α,α-dimethyl-δ-phthalimidolevulinate (6.2 g., 17.6%), m.p. 126–127°, and methyl β,β-dimethyl-δ-phthalimidolevulinate (6.5 g., 18.4%), m.p. 80°.

Dimethylphthalimidolevulinic Acids.—Methyl α,α-dimethyl-δ-phthalimidolevulinate, m.p. 126–127° (300 mg.), and 10 ml. of 8.4 *N* hydrochloric acid were refluxed. Hydrolysis to the extent of 17.5% (based on the phthalimidolevulinic acid obtained) took place during 5 min. of refluxing, to the extent of 86% during

15 min. of refluxing. α,α-Dimethyl-δ-phthalimidolevulinic acid was recrystallized from acetone–water, m.p. 159–160°.

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.29; H, 5.27; N, 4.84. Found: C, 62.24; H, 5.34; N, 5.07.

Methyl β,β-dimethyl-δ-phthalimidolevulinate under the same conditions hydrolyzed to the extent of 64.8% during 5-min. reflux to yield β,β-dimethyl-δ-phthalimidolevulinic acid. It was recrystallized from acetone–water, m.p. 157–158°.

Anal. Found: C, 61.99; H, 5.41; N, 4.89.

A mixture of these two isomeric acids melted at 130–137°.

α,α-Dimethyl-δ-aminolevulinic Acid.—Methyl α,α-dimethyl-δ-phthalimidolevulinate (5 g.) and 55 ml. of 24% hydrobromic acid were refluxed for 12 hr. The α,α-dimethyl-δ-aminolevulinic acid hydrobromide obtained was recrystallized from a methanol–acetone–ether mixture to yield colorless crystals, 3.65 g. (92.1%), m.p. 150°. The yield of phthalic acid was 2.60 g. (95%).

Anal. Calcd. for $C_7H_{14}BrNO_3$: C, 35.02; H, 5.88; Br, 33.28; N, 5.83. Found: C, 34.89; H, 5.91; Br, 33.54; N, 6.02.

α,α-Dimethyl-δ-aminolevulinic acid hydrochloride was obtained as highly hygroscopic crystals. To a solution of the amino acid hydrochloride (obtained from the hydrolysis of 2.0 g. of phthalimidolevulinate) in 10 ml. of water was added a solution of 1.3 g. of disodium naphthalene-1,5-disulfonate in 15 ml. of water. The solution was warmed on the steam bath for a few minutes and allowed to cool gradually. Colorless needles of the disulfonate salt separated. It was recrystallized once again from water. It started charring at 258° and completely blackened at 262°. The yield (1.8 g.) was 90%.

Anal. Calcd. for $(C_7H_{14}NO_3)_2 \cdot C_{10}H_6O_6S_2$: C, 47.48; H, 5.65; N, 4.62. Found: C, 47.70; H, 5.63; N, 4.58; S, 10.76.

β,β-Dimethyl-δ-aminolevulinic Acid Hydrochloride.—Methyl β,β-dimethyl-δ-phthalimidolevulinate, m.p. 80° (3.7 g.), and 45 ml. of 6 *N* hydrochloric acid were refluxed for 12 hr. The yield of phthalic acid was 1.9 g. (94%). The β,β-dimethyl-δ-aminolevulinic acid hydrochloride obtained was recrystallized from an acetone–methanol–ether mixture to yield colorless crystals, 2.05 g. (86%), m.p. 182°.

Anal. Calcd. for $C_7H_{14}ClNO_3$: C, 42.96; H, 7.21; Cl, 18.12; N, 6.99. Found: C, 42.85; H, 7.14; Cl, 18.17; N, 6.96.

Methyl β,δ-Dimethyl-δ-chlorolevulinates.—β-Carbomethoxyisobutyryl chloride (25 g.) was treated with diazoethane prepared from 70 g. of N-nitrosoethyl urea. This was followed by treatment with dry hydrogen chloride for 3 hr. as usual. A small amount of ether-insoluble, water-soluble, yellow, powdery mass which formed was filtered off. The dark brown liquid product was distilled. A yellow oil boiling over a range of 53–73° (0.5 mm.), $n^{27.5}D$ 1.4370–1.4480, was obtained. The yield was 14.25 g. The main fraction (12.0 g.) was redistilled and boiled at 55–63° (0.3 mm.), $n^{29}D$ 1.4380–1.4420. A portion of the main fraction of this distillation was redistilled for analysis. The major fraction, b.p. 52° (0.1 mm.), $n^{29}D$ 1.4415, $d^{28.5}$ 1.1057, was yellow and obviously impure.

Anal. Calcd. for $C_8H_{13}ClO_3$: C, 49.90; H, 6.77; Cl, 18.41. Found: C, 52.73; H, 7.39; Cl, 14.69.

The infrared spectrum showed no olefinic peaks even though analysis indicated some dehydrochlorination. The n.m.r. spectrum of the analytical sample showed two doublets of equal intensity at τ 8.57 and 9.0 (J = 7.2 c.p.s.) for the two CH_3CH groups (the doublet at the lower intensity showed fine splitting into four peaks); a multiplet at τ 6.7–8 for the CH_2CH– group; a singlet at τ 6.7 for OCH_3; and a finely split quadruplet at τ 5.6 for the CHCl group.

Phthalimido Derivatives.—The mixture containing methyl β,δ-dimethyl-δ-chlorolevulinate obtained after three distillations (b.p. 56–68° at 0.3 mm.) was treated with potassium phthalimide in dimethylformamide during 1 hr. at room temperature at 100° for 5 hr. In a subsequent experiment the chloro ester, obtained after one distillation, b.p. 70–90° (1 mm.), was treated likewise with potassium phthalimide at room temperature for 20 hr. The reaction mixtures were worked up as usual to yield a semisolid residue; this was taken up in methanol–petroleum ether (30–60°) and cooled. A crystalline solid separated in 16–20% yield and was recrystallized from ethyl acetate–petroleum ether (30–60°) to yield colorless plates, m.p. 125°.

Anal. Calcd. for $C_{16}H_{17}NO_5$; C, 63.37; H, 5.65; N, 4.62. Found: C, 63.28; H, 5.84; N, 4.62.

The infrared spectrum was similar to the other phthalimidolevulinates. The n.m.r. spectrum of the compound showed a single doublet for the CH_3 group at τ 8.92 (three protons), indicating that only one CH_3CH group remains in the molecule. We conclude that the compound is **methyl 3-methyl-4-oxo-6-phthalimidohexanoate**, since this structure fully explains the complex multiplet between τ 7 and 8 (five protons, $—CH_2COCHCH_2—$), the sharp singlet at τ 6.5 (three protons, OCH_3), the triplet at τ 6.2 (two protons, $>N—CH_2—$), and the doublet at τ 2.5 (four protons).

Hydrolysis.—The phthalimido derivative, m.p. 125°, on hydrolysis with 6 *N* hydrochloric acid during 5-min. reflux gave **3-methyl-4-oxo-6-phthalimidohexanoic acid**. It was recrystallized from ethyl acetate–petroleum ether, m.p. 150°.

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.29; H, 5.27; N, 4.87. Found: C, 62.46; H, 5.38; N, 4.78.

6-Amino-3-methyl-4-oxohexanoic Acid Hydrochloride.—The phthalimido derivative, m.p. 125° (1.0 g.), was refluxed with 15 ml. of 6 *N* hydrochloric acid for 8 hr. The product was recrystallized from a mixture of acetone, methanol, and ether to yield 0.60 g. (93.3%) of colorless crystals, m.p. 125–126°.

Anal. Calcd. for $C_7H_{14}ClNO_3$: C, 42.96; H, 7.21; Cl, 18.12; N, 6.99. Found: C, 42.93; H, 7.17; Cl, 18.08; N, 7.02.

Pyrolysis Studies. XV. Thermal Retrograde Aldol Condensation of β-Hydroxy Ketones[1a]

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This present note reports the vapor phase kinetics of a retrograde aldol condensation of 4-hydroxy-4-methyl-2-pentanone which thermally decomposes to acetone. In a very well-seasoned reactor this compound decomposes by first-order kinetics with a negative entropy of activation (−8.3 ± 1.5 e.u. at 220°) and an activation energy of 31.2 ± 1.0 kcal./mole. The reaction was shown to be homogeneous on changing the surface to volume ratio ten times by introducing a stainless steel sponge. The values of the rate constant before and after packing were 8.77×10^{-3} and 8.98×10^{-3} sec.$^{-1}$, respectively, at 243.9°. It proved difficult to obtain reproducible kinetic results, thus requiring extended treatments with 3-butenoic acid at 400° and repeated pyrolyses (50 times) of the β-hydroxy ketone to completely deactivate the walls of the stainless steel reactor. Interestingly, first-order plots of $(P_\infty - P_t)$ against time were linear up to at least 90% decomposition before the surface was completely deactivated. Normally the plots are curved when a heterogeneous reaction is occurring. Eventually reproducible results were obtained and first-order plots were linear to greater than 90% completion.

Although this vapor phase reaction was reported in Hurd's[2] book on pyrolysis, very little has been reported since as has nothing on the mechanism of the reaction.

Based on the kinetics obtained and the products formed it is proposed that β-hydroxy ketones thermally decompose in the vapor state through a six-membered cyclic transition state mechanism (I) similar to those

(1) (a) This paper was presented in part at the Northwest Regional Meeting of the American Chemical Society in Spokane, Wash., June 1964. (b) Postdoctoral research associate, 1963–1964.

(2) C. D. Hurd, "The Pyrolysis of Organic Compounds," The Chemical Catalog Co., Inc., Reinhold Publishing Corp., New York, N. Y., 1929, p. 164.