TABLE 1
THERMAL DECOMPOSITION OF II

Additive	Temp. of rapid dec., °C.	Total oxazoline yield, %
None	185	60
NH_4Cl	140	65
NH_4ClO_4	130	55
p-$CH_3C_6H_4SO_3H$	145	58
H_2SO_4	140	65
H_3PO_4	130	60
NaOMe	185	30
KOH	210	25

propyl butyrate, was obtained as an oil in 54% yield. It showed infrared absorption bands at 5.80 (ester), 8.00 (P=O), 3.00, and 3.12 μ (NH).

Anal. Calcd. for $C_{21}H_{42}N_3O_7P$: C, 52.59; H, 8.82; N, 8.76; P, 6.48. Found: C, 52.31; H, 8.21; N, 9.02; P, 6.83.

Hydrolysis of II.—A solution of II in 25% sodium hydroxide was heated at reflux for 12 hr. Continuous ether extraction gave a mixture of 1-amino-2-propanol and 2-amino-1-propanol, identified by their retention times on a Carbowax–Haloport-F gas chromatography column. From the relative peak areas, it was estimated that the mixture contained 40% of the former and 60% of the latter; more accurate analysis was not attempted.

Reaction of II with Butyric Acid.—A mixture of 48 g. (0.1 mole) of II and 40 ml. (0.43 mole) of butyric acid was heated at 150° in an oil bath for 3 hr. The product was dissolved in ether and washed with sodium bicarbonate solution, and the ether was dried and evaporated. The product, a mixture of the ester amides III and IV, was then distilled: b.p. 125° (1 mm.), yield 40 g. (62%). The infrared spectrum showed bands at 5.75 (ester) and 6.02 μ (amide).

Anal. Calcd. for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.82; N, 6.50; O, 22.29. Found: C, 60.64; H, 9.57; N, 6.38; O, 22.33.

The product was hydrolyzed by heating with 100 ml. of 8% sodium hydroxide solution for 5 hr. Continuous ether extraction gave 14 g. (52% yield) of a mixture of the hydroxyamides, V and VI. Three grams of this mixture was heated with 4 g. of 3,5-dinitrobenzoyl chloride, and by fractional crystallization the 3,5-dinitrobenzoates of V, m.p. 129–130°, and of VI, m.p. 180–182°, were separated. Mixture melting point determinations showed them to be the same as authentic derivatives. Acidification of the sodium hydroxide solution gave butyric acid.

Thermal Decomposition of II.—Twenty-three grams of II (0.048 mole) was placed in a 200-ml. distillation flask at 1mm. The flask was then gradually heated in an oil bath (*ca.* 1°/min.) until the temperature inside the flask reached 185°. At this temperature the material became cloudy. The temperature was then held constant, and the decomposition became very rapid within about 10 min. as evidenced by the formation of large amounts of vapor. The decomposition was complete in 30 min. The product was collected in a Dry Ice cooled receiver and was analyzed by gas chromatography using a Ucon Polar column with xylene as an internal standard. It contained 7.1 g. (40% yield) of 2-propyl-4-methyl-Δ^2-oxazoline (VIII), 3.5 g. (20% yield) of 2-propyl-5-methyl-Δ^2-oxazoline (VII), and 0.8 g. (12% yield based on reaction 3) of a mixture of the butyramides (V and VI) of 1-amino-2-propanol and 2-amino-1-propanol. The ratio of the two oxazolines was the same when unpurified II was decomposed. The oxazoline isomers VII and VIII were separated by fractionation on a Todd column. Each was then reacted at room temperature with 3,5-dinitrobenzoyl chloride in sodium bicarbonate solution[9] to form 1-(3,5-dinitrobenzamido)-2-propyl butyrate, m.p. 140–141°, and 2-(3,5-dinitrobenzamido)-1-propyl butyrate, m.p. 82–83°, respectively. These derivatives did not depress the melting points of the corresponding derivatives from authentic oxazoline samples. The oxazoline products were also identical with authentic samples in boiling points and infrared spectra. The pot residue was an amorphous solid which readily dissolved in water to form an acidic solution.

A series of decomposition experiments was carried out in a manner similar to that described above in which 5% of various acids or bases were mixed with II prior to decomposition. The results are shown in Table I.

1-Butyramido-2-propanol (V).—A mixture of 15 g. (0.2 mole) of 1-amino-2-propanol and 25 g. (0.2 mole) of n-butyl butyrate was heated in an oil bath at reflux temperature for 6 hr. The butyl alcohol was then removed under reduced pressure and the product was distilled: b.p. 166° (10 mm.), yield 45%. A 3,5-dinitrobenzoate was prepared by heating the product with 3,5-dinitrobenzoyl chloride; it had m.p. 130–131° (alcohol–water).

Anal. Calcd. for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38 Found: C, 49.60; H, 4.78; N, 12.78.

2-Butyramido-1-propanol (VI).—This product was prepared by heating at reflux a mixture of 10 g. (0.13 mole) of 2-amino-1-propanol[12] and 21 g. (0.14 mole) of n-butyl butyrate. The product was obtained in 30% yield: b.p. 126° (mm.), 3,5-dinitrobenzoate m.p. 182–184° (alcohol).

Anal. Calcd. for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.63; H, 4.99; N, 12.13.

2-Propyl-5-methyl-Δ^2-oxazoline (VII).—This material was prepared from V by a procedure similar to that described by Wenker.[13] The yield was 25%, b.p. 150°, infrared band at 5.95 μ (N=C).

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.02. Found: C, 65.57; H, 9.67; N, 10.79.

The product was converted to 1-(3,5-dinitrobenzamido)-2-propylbutyrate by stirring with 3,5-dinitrobenzoyl chloride in sodium bicarbonate solution; it had m.p. 139–141° (alcohol–water).

Anal. Calcd. for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.30; H, 4.81; N, 11.97.

2-Propyl-4-methyl-Δ^2-oxazoline (VIII).—This oxazoline was prepared from VI.[13] The yield was 32%, b.p. 145°, infrared absorption at 5.95 μ (N=C).

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.02. Found: C, 65.92; H, 10.00; N, 10.94.

2-(3,4-Dinitrobenzamido)-1-propyl butyrate from VIII and 3,5-dinitrobenzoyl chloride underwent reaction in sodium bicarbonate solution giving a product with m.p. 84–85° (alcohol–water).

Anal. Calcd. for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.63; H, 5.05; N, 12.37.

(12) F. F. Blicke, J. A. Faust, R. J. Warzynski, and J. E. Gearien, *J. Am. Chem. Soc.*, **67**, 205 (1945).

(13) H. Wenker, *ibid.*, **57**, 1079 (1935).

The pK_a Values of Some 2-Aminomidazolium Ions

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In his book on imidazole and its derivatives, Hofmann[1] states that the properties of 2-aminoimidazole demonstrate that it is best regarded as a guanidine derivative, the 2-aminoimidazolium ion receiving major contributions from structures with the positive charge evenly distributed among all three nitrogens. It is just this even distribution of positive charge which makes guanidine a strong base[2]; major contributions from such structures should result in high basicity for 2-aminoimidazole and its derivatives compared to imidazole. If the 2-aminomidazoles were strong enough bases to be considered derivatives of guanidine rather than of imidazole, it would imply that an amino substituent at the 2-position of the imidazole ring could profoundly alter the imidazole structure. Such an alteration seemed very unlikely. The study reported

(1) K. Hofmann, "The Chemistry of Heterocyclic Compounds," Vol. 6, A. Weissburger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp. 141, 142.

(2) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 96.

here was undertaken to check this point by determining the pK_a values of some 2-aminoimidazolium ions.

2-Aminoimidazolium sulfate and 1-methyl-2-aminoimidazolium chloride were prepared from the appropriate guanidino acetals by the method of Lawson.[3] The sulfate salt of 2-aminoimidazole is not hygroscopic and is easy to purify, whereas the chloride salt is very hygroscopic and difficult to work with. 4,5-Dimethyl-2-aminoimidazolium chloride was prepared according to Pyman's method[4] from the imidazole by coupling with *p*-bromobenzene diazonium chloride followed by hydrogenation. The four 4,5-diaryl-2-aminoimidazoles were prepared by hydrogenation of the corresponding bishydrazo compounds according to the synthesis worked out by Kreutzberger[5]; they were isolated as the free bases.

The pK_a values were determined for 2-aminoimidazolium ion and the two methyl-substituted derivatives in 0.1 *N* aqueous KCl solution. The values for the four 4,5-diaryl-2-aminoimidazolium ions were determined in a 1:1 (v./v.) ethanol–0.1 *N* aqueous KCl solution because the free base forms of these ions were not soluble in water. For comparison, the pK_a values of the water-soluble compounds were also measured in the mixed solvent. The value for imidazole itself was measured in both solvents as a control. The values obtained are reported in Table I, as well as literature values.[6-8]

TABLE I

pK_a VALUES FOR SOME 2-AMINOIMIDAZOLIUM IONS AT 25.0° DETERMINED IN WATER AND ETHANOL–WATER SOLUTIONS OF POTASSIUM CHLORIDE

	pK_a[a]	
Cation	0.1 *N* KCl	0.1 *N* KCl–EtOH 1:1 (v./v.)
2-Aminoimidazolium[b]	8.46	8.39
1-Methyl-2-aminoimidazolium[c]	8.65	8.44
4,5-Dimethyl-2-aminoimidazolium[d]	9.21	8.88
4,5-Diphenyl-2-aminomidazolium[e]	...	7.04
4,5-Di(4-methoxyphenyl)-2-aminoimidazolium[e]	...	7.38
4,5-Di(2-pyridyl)-2-aminoimidazolium[e]	...	6.95
4,5-Di(6-methyl-2-pyridyl)-2-aminoimidazolium[e]	...	7.33
Imidazolium[e]	7.01[f]	6.34

[a] Precision of determination ±0.02 unit. [b] Sulfate salt. This salt is not hygroscopic; the hydrochloride is. [c] Chloride monohydrate salt. [d] Chloride salt. [e] Free base titrated with standard HCl. [f] Lit. 6.95,[6] 7.03,[7] 7.09.[8]

It is evident from the values in the table that 2-aminoimidazoles are best regarded as substituted imidazoles, not derivatives of guanidine. The 2-amino substituent does not have any profound effect on the imidazole structure, as expected. It does result in a pK_a value for the 2-aminoimidazolium ion nearly 1.5 units greater than that of imidazolium ion in 0.1 *N* KCl at 25°, but a 2-methyl substituent has nearly the same effect; 2-methylimidazolium ion has a pK_a value of 7.86 under the same conditions,[6] an increase of 0.9 unit.

(3) A. Lawson, *J. Chem. Soc.*, 307 (1956).
(4) R. Burtles and F. L. Pyman, *ibid.* 2012 (1925).
(5) A. Kreutzberger, *J. Org. Chem.*, **27**, 886 (1962).
(6) A. H. M. Kirby and A. Neuberger, *Biochem. J.*, **32**, 1146 (1938).
(7) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962, Table 8.11, p. 145. These authors give ref. 6 above as the source of their value, but do not explain the discrepancy between their tabulated value and the value given in ref. 6.
(8) B. L. Mickel and A. C. Andrews, *J. Am. Chem. Soc.*, **77**, 5291 (1955).

Experimental

Melting points were obtained with a Hoover capillary melting point apparatus (Arthur H. Thomas, Philadelphia). Elemental analyses were carried out by Mr. Clyde W. Nash of these laboratories.

2-Aminoimidazolium Sulfate.—Aminoacetaldehyde diethyl acetal (25 g., 0.187 mole), 40 ml. of water, and 25 g. of S-methyl isothiourea sulfate (0.180 mole) were heated together at 90° for 1 hr. The water was removed to give an oil which was dissolved in methanol; precipitation with acetone gave 31 g. (77%) of N-(2,2 diethoxyethyl)guanidine sulfate, m.p. 148–152°.

Anal. Calcd. for $C_{14}H_{36}N_6O_8S$: C, 37.50; H, 8.04; N, 18.80; S, 7.14. Found: C, 37.03; H: 7.97; N, 18.15; S, 7.88.

N-(2,2 Diethoxyethyl)guanidine sulfate (10 g., 0.045 mole) and 6 ml. of concentrated HCl were warmed on the steam bath for 15 min. 30 ml. of water was added, and the solution was evaporated to a sirup. Another 30 ml. of water was added, and the solution was again evaporated to dryness. The sirup was dissolved in 25 ml. of absolute ethanol and the salt was precipitated with absolute ether to give 2.3 g. of product, m.p. 275–278°, 39% yield.

Anal. Calcd. for $C_6H_{12}N_6.SO_4$: C, 27.30; H, 4.54; N, 31.80; SO_4, 36.30. Found: C, 27.34; H, 4.76; N, 31.82; SO_4 35.85.

1-Methyl-2-aminoimidazolium Chloride Monohydrate.—N-Methylaminoacetaldehyde dimethyl acetal (10 g., 0.068 mole), 22 g. of 50% aqueous cyanamide solution (0.26 mole cyanamide), and 4 g. acetic of acid (0.068 mole) were stirred for 1 hr. at 40–50°. The mixture was evaporated to a syrup which was triturated with ether. Acetone was then added to give 8 g. (47.3%) of N-(2,2 diethoxyethyl)-N-methylguanidine acetate as beautiful plates. Recrystallization from ethanol–ethyl acetate afforded plates, m.p. 200–201°.

Anal. Calcd. for $C_{10}H_{23}N_3O_4$: C, 48.20; H, 9.24; N, 16.88. Found: C, 48.36; H, 9.44; N, 16.64.

A mixture of 3.3 g. of N-(2,2-diethoxyethyl)-N-methylguanidine acetate (0.0133 mole) was warmed with 3 ml. of concentrated HCl. The mixture was twice treated with 10 ml. of water and evaporated to dryness. The resulting sirup was dissolved in ethanol and precipitated with ethyl acetate to give 1.3 g. of 1-methyl-2-aminoimidazolium chloride monohydrate (73%), m.p. 84–85°.

Anal. Calcd. for $C_4H_{10}ClN_3O$: C, 31.68; H, 6.67; Cl, 23.39; N, 27.71. Found: C, 31.90; H, 6.68; Cl. 23.05; N, 27.98.

4,5-Dimethyl-2-aminoimidazolium Chloride.—Acetoin (50 g., 0.57 mole) and 250 ml. of formamide were refluxed for 4 hr. Distillation of the mixture gave 12 g. of 4,5-dimethylimidazole (21%), b.p. 160° at 2 mm., m.p. 85–90°. Recrystallization from dioxane afforded needles, m.p. 90°, hydrochloride m.p. 301–302° (lit.[9] m.p. 305°). A solution of 6 g. of 4,5-dimethylimidazole (0.063 mole) and 96 g. of Na_2CO_3 in 640 ml. of water was added to a solution of *p*-bromobenzenediazonium chloride, which had been prepared by reacting 11 g. of *p*-bromoaniline (0.064 mole) in 64 ml. of concentrated HCl and 190 ml. of water with 4.6 g. of $NaNO_2$ in 23 ml. of water at 0° for 15 min. The crude product was collected as a brown solid after the mixture had stood for 6 hr. The crude coupling product was used as is; recrystallization of a small sample from ethanol gave needles of 2-(*p*-bromobenzeneazo)-4,5-dimethylimidazole, m.p. 219–220° (lit.[4] m.p. 213–214°). The crude azo compound (31 g.) was stirred with 64.2 g. of $SnCl_2$ in 149 ml. of concentrated HCl and 575 ml. of water at 90° until the brown color was discharged. Then H_2S was passed into the solution until precipitation of stannic sulfide was complete. The mixture was filtered; the filtrate was reduced in volume by evaporation, made alkaline, and refiltered. The filtrate was washed with ether, acidified with HCl, and evaporated to dryness. Extraction of the residue with 150 ml. of ethanol and concentration of the ethanol solution to a volume of 30 ml. gave, on cooling, 12 g. (71%) of crude 4,5-dimethyl-2-aminoimidazolium chloride, m.p. 280–290°. Recrystallization from ethanol gave needles, m.p. 289–292° (lit.[4] m.p. 289°).

Anal. Calcd. for $C_5H_{10}ClN_3$: C, 40.70; H, 6.78; Cl, 24.06; N, 28.46. Found: C, 40.60; H, 7.02; Cl, 24.33; N, 28.17.

4,5-Diphenyl-2-aminoimidazole.—This compound was prepared by hydrogenation of the 2,2′-hydrazoimidazole formed

(9) H. Biedereck and G. Theilig, *Chem. Ber.*, **86**, 88 (1953).

from benzoin and 1,2 hydrazinedicarboxyamidine, using the method of Kreutzberger, and was recrystallized from ethanol, m.p. 256–260° (lit.[5] m.p. 233–234°).

Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H,5.57; N, 17.86; equiv. wt., 235. Found: C, 76.60; H, 5.45; N, 17.86; equiv. wt., 234.

4,5-Di(4-methoxyphenyl)-2-aminoimidazole.—This compound was prepared from anisoin as described above, and was recrystallized from ethanol, m.p. 245–248° (lit.[5] m.p. 225–226°).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.15; H, 5.76; N, 14.24; equiv. wt., 295. Found: C, 69.91; H, 5.98; N, 14.31; equiv. wt., 298.

4,5-Di(2-pyridyl)-2-aminoimidazole, recrystallized from acetone, had m.p. 238–240° (lit.[5] m.p. 230–231°).

Anal. Calcd. for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52; equiv. wt., 239. Found: C, 65.63; H, 4.86; N, 29.79; equiv. wt., 238.

4,5-Di-(6-methyl-2-pyridyl)-2-aminoimidazole, recrystallized from ethanol, had m.p. 263–266° (equiv. wt.: calcd., 265; found, 267). This compound was very prone to autooxidation and consistent elemental analyses could not be obtained. The infrared spectrum and the equivalent weight of a freshly recrystallized sample showed that such a sample was indeed the compound in a high state of purity. All samples used for pK_a measurements were freshly recrystallized just prior to the run.

pK_a Determinations.—Solutions of the unsubstituted and alkyl-substituted 2-aminoimidazolium salts were prepared at a concentration of about 8×10^{-3} *M* in 0.10 *N* KCl and in 1:1 (v./v.) 0.10 *N* KCl–ethanol solutions. These salts were titrated with 0.10 *N* NaOH. The diaryl compounds were not soluble in water; they were prepared as solutions of the free base form at about 8×10^{-3} *M* in the 0.10 *N* KCl–ethanol solution, and titrated with 0.10 *N* HCl. The pH determinations were made with a Beckman pH meter (Model G) equipped with a glass electrode and a sealed calomel electrode. Titrations were carried out at 25.0° in a constant-temperature bath; the solutions being titrated were stirred with a magnetic stirrer. The pK_a values were calculated from the titration curves. The meter was calibrated against standard 0.10 *N* HCl and 0.10 *N* NaOH. The correction in the pH reading was independent of the actual pH. Blank titrations of KCl and KNO_3 at the same concentrations used for the imidazolium salts were carried out with both the acid and base titrant to check the procedure and to make sure that the small amount of added salt did not affect the meter calibration. From the base titration of KCl as a blank, a pK_w of 13.79 was calculated; with KNO_3 the value was 13.80, in good agreement with the value of 13.78 calculated for these conditions.[10] In the ethanolic system, the pK_w values obtained from the blank titrations were 14.72 and 14.73, respectively.

(10) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd Ed., Reinhold Publishing Corp., New York, N. Y. 1950, pp. 481–486.

The Thermal Decomposition of Dialkyl Chelidamates and Related Esters

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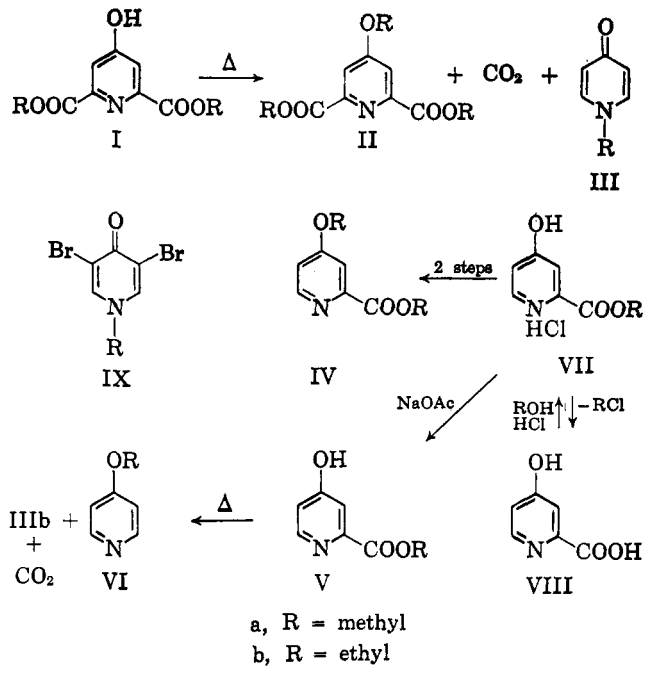
Recently it was observed in this laboratory that dimethyl 4-hydroxydipicolinate (Ia) when heated to 200–210° lost carbon dioxide and was converted to a mixture containing dimethyl 4-methoxypyr dine-2,6-dicarboxylate (IIa) and N-methyl-4-pyridone (IIIa). Additional, tarry decomposition products were also formed but not further investigated. The decomposition of diethyl 4-hydroxydipicolinate (Ib) proceeded similarly although a slightly higher reaction temperature was required. Also, in addition to the expected



a, R = methyl
b, R = ethyl

diethyl 4-ethoxypyridine-2,6-dicarboxylate (IIb) and N-ethyl-4-pyridone (IIIb) some ethyl 4-ethoxypicolinate (IVb) was isolated. The pyrolysis of ethyl 4-hydroxypicolinate (Vb) produced predominantly N-ethyl-4-pyridone and a small amount of 4-ethoxypyridine (VIb). No ethyl 4-ethoxypicolinate was isolated from this reaction. In contrast to these results, ethyl 4-hydroxypicolinate hydrochloride (VIIb) decomposed to ethyl chloride and 4-hydroxypicolinic acid (VIII) when it was heated to 180–210°.

Ethyl 4-ethoxypicolinate (IVb), which was obtained in small quantity on pyrolysis of diethyl 4-hydroxydipicolinate, was also synthesized from 4-hydroxypicolinic acid (VIII) by esterification and replacement of the hydroxyl by chlorine and, subsequently, by an ethoxy group.

Since N-alkyl-4-pyridones are hygroscopic substances,[1] they were converted to derivatives for identification. In this connection it was observed that the melting point of N-ethyl-3,5-dibromo-4-pyridone differs considerably from the one stated in the literature.[2] No analytical data for this compound are included in the paper cited, whereas satisfactory values were obtained for the material prepared during this investigation. Therefore, the melting point of N-ethyl-3,5-dibromo-4-pyridone (IXb) given in the experimental part is probably more nearly the correct one.

Experimental[3]

Decomposition of Dimethyl 4-Hydroxydipicolinate.[4]—A batch of 11.7 g. (0.055 mole) of this ester was placed in a small distilling flask and immersed in a metal bath which was preheated to 210°. This temperature was maintained for 75 min. while carbon dioxide (0.071 mole) was evolved. After this period of time the evolution of gas had ceased and the residue in the flask was distilled. Fractions of boiling range 150–182° at 2 mm. (4.3 g.) and 183–189° at 2 mm. (2.1 g.) were collected. The lower boiling

(1) D. G. Markees, *J. Org. Chem.*, **23**, 1030 (1958).
(2) T. Ishii, *J. Pharm. Soc. Japan*, **71**, 1092 (1951).
(3) All melting points were determined on a Mel-Temp apparatus and are corrected. The boiling points are not corrected.
(4) L. R. Fibel and P. E. Spoerri, *J. Am. Chem. Soc.*, **70**, 3908 (1948).