TABLE I

URANYL DIALKYLDITHIOCARBAMATES, $UO_2(R_2NCS_2)_2 \cdot XC_2H_5OH$

R	Empirical formula	Ethanol of crystln., moles	Yield, %	M.p., °C.	Uranium, % Calcd.	Uranium, % Found	Sulfur, % Calcd.	Sulfur, % Found
C_2H_5	$C_{18}H_{44}N_2O_6S_4U$	4	24	Dec.	31.7	30.9	17.1	17.4
Piperidyl	$C_{24}H_{56}N_2O_8S_4U$	6	30	>250	28.4	29.3		
$CH_2{=}CHCH_2$	$C_{26}H_{44}N_2O_8S_4U$	6	14	156	27.1	27.3	14.5	14.4
C_3H_7	$C_{26}H_{50}N_2O_8S_4U$	6	13	186	26.9	27.2	14.5	15.4
n-C_4H_9	$C_{30}H_{72}N_2O_8S_4U$	6	13	154	24.9	24.9	13.4	14.3
i-C_4H_9	$C_{30}H_{72}N_2O_8S_4U$	6	14	188	24.9	24.9	13.4	13.5
s-C_4H_9	$C_{30}H_{72}N_2O_8S_4U$	6	18	194	24.9	24.8	13.4	13.4

Uranyl *t*-Butoxide.—A solution of uranium(IV) *t*-butoxide[6] in petroleum ether (b.p. 28–38°) was allowed to stand in the presence of dry air for three days. During this time the solution changed color from bright green to bright red. When the red solution was allowed to evaporate slowly, hard red crystals were obtained. The same red compound was formed when dry oxygen was slowly bubbled through a solution of uranium(IV) *t*-butoxide in petroleum ether. The solution changed from green to brown and finally red, and upon evaporation a red crystalline solid was obtained.

When uranium(IV) *t*-butoxide was heated under greatly reduced pressure, a red sublimate was obtained. This was partially soluble in petroleum ether, and when the resulting solution was evaporated, it deposited a red crystalline solid.

Unfortunately, no carbon and hydrogen analyses were carried out. Six uranium analyses on samples prepared by each of the above processes gave values in the range 32.0–32.4% uranium. Calcd. for $UO_2(OC_4H_9)_2 \cdot 4C_4H_9OH$: U, 32.02.

AMES, IOWA

(6) R. G. Jones, G. Karmas, G. A. Martin, Jr., and H. Gilman, THIS JOURNAL, **78**, 4285 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Metalation of 1-Methyl-, 1-Benzyl- and 1-Phenylimidazole with *n*-Butyllithium

BY DAVID A. SHIRLEY AND PEGGY W. ALLEY

RECEIVED APRIL 10, 1957

1-Methyl-, 1-benzyl- and 1-phenylimidazole are metalated in the 2-position with *n*-butyllithium in yields above 65%. 1-Methylimidazole was found to give a small amount of metalation in the 5-position. Dimetalation of 1-phenylimidazole followed by carbonation gave in low yield a cyclic ketone, 4-oxoimidazo[1,2-a]indoline, a new heterocyclic ring system. The 2-lithioimidazoles from metalation were converted to a variety of derivatives.

The metalation of heterocyclic ring systems by organolithium reagents is frequently a useful method of placing substituents in positions not available in substitution by most reagents. The metalation in the 2-position of thianaphthene[1] and N-substituted indoles,[2] the 1-position of phenothiazine,[3] the 4-position of dibenzofuran[4] and phenoxathiin[5] are examples of monosubstitution of positions not reached by other substitution reactions. We have extended our examination of the metalation of heterocyclic ring systems to some N-substituted imidazoles.

Imidazole and its N-substituted derivatives undergo nitration, chlorination, bromination and sulfonation in the 4- and/or 5-positions. In the case of chlorination and bromination, 2-substitution occurs after substitution of the 4- and 5-positions. At least three reactions, however, allow substitution preferentially in the 2-position. These are iodination, hydroxymethylation and diazo coupling.[6]

The strong tendency for metalation to occur at positions adjacent to the hetero atom in heterocyclic rings is well-established.[7] There are few reports, however, of metalation of monocyclic systems containing two hetero atoms. The metalation of thiazole[8] and 4,5-dimethylthiazole[9] in the 2-position with phenyllithium and the metalation of 1-phenyl-3-methylpyrazole with *n*-butyllithium in the 5-position[10] appear to be the only recorded examples.

Metalation of 1-methylimidazole with an equivalent of *n*-butyllithium followed by carbonation produced mainly 1-methyl-2-imidazolecarboxylic acid (32% yield) and a small amount (1.5% yield) of the 5-acid. The structure of the 5-acid was indicated by comparison of the melting point of the picrate of the acid and the picrate of the methyl ester with values given by Hubball and Pyman[11] and also by comparison of the picrate of the methyl ester with an authentic sample prepared from methyl 1-methyl-2-mercapto-5-imidazolecarboxylate. 1-Methyl-2-imidazolecarboxylic acid has not been reported previously. Its structure was proved by two lines of evidence. First the picrate of the methyl ester of 1-methyl-4-imidazolecarboxylic acid, m.p. 171–172°, has been described by Hubball and Pyman,[11] while the picrate of the methyl

(1) D. A. Shirley and M. D. Cameron, THIS JOURNAL, **72**, 2788 (1950).

(2) D. A. Shirley and P. A. Roussel, *ibid.*, **75**, 375 (1953).

(3) H. Gilman, D. A. Shirley and P. R. Van Ess, *ibid.*, **66**, 625 (1944).

(4) H. Gilman, F. W. Moore and O. Baine, *ibid.*, **63**, 2479 (1941).

(5) H. Gilman, M. Van Ess, H. B. Willis and F. J. Webb, *ibid.*, **62**, 2606 (1940).

(6) K. Hofmann, "Imidazole and its Derivatives," Part 1, Interscience Publishers, Inc., New York, N. Y., 1953.

(7) H. Gilman and J. W. Morton in R. Adams, ed., "Organic Reaction," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 258–304.

(8) J. Metzger and B. Koether, *Bull. soc. chim. France*, 702 (1953).

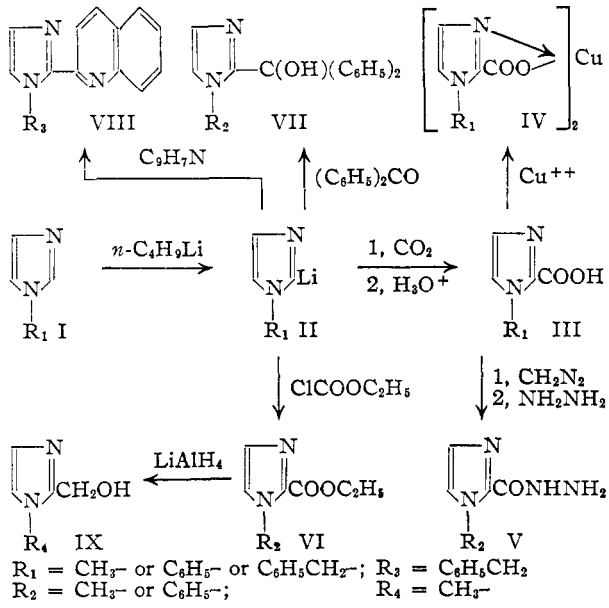
(9) M. Erne and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 652 (1948).

(10) H. R. Snyder, F. Verbanc and D. B. Bright, THIS JOURNAL, **74**, 3246 (1952).

(11) W. Hubball and F. L. Pyman, *J. Chem. Soc.*, 21 (1928).

ester of the acid obtained from metalation melted at 143–145°. Secondly, the metalation of 1-methylimidazole and addition of ethyl chloroformate gave ethyl 1-methyl-2-imidazolecarboxylate (VI, Scheme I) which was reduced with lithium

SCHEME I



R_1 = CH_3– or C_6H_5– or $C_6H_5CH_2$–; R_3 = $C_6H_5CH_2$
R_2 = CH_3– or C_6H_5–; R_4 = CH_3–

aluminum hydride to the known[12] 1-methyl-2-hydroxymethylimidazole. A picrate of the hydroxymethyl derivative melted at 139–140° compared with the reported[12] value of 138°. Since the yield of VI (R_2 = CH_3) was only about 10% after considerable loss during purification, it was converted to the corresponding hydrazide which was shown to be identical with the hydrazide from the metalation acid (III).

During the isolation of the picrate of 1-methyl-2-hydroxymethylimidazole, a second picrate, m.p. 145–146°, was isolated. This showed elemental analytical values close to the first picrate (m.p. 139–140°), but a mixed m.p. gave a sharp depression. The second picrate was shown to be a 1:1 molecular compound of the picrate of 1-methylimidazole and 1-methyl-2-hydroxymethylimidazole. This compound has been reported by Grindley and Pyman[12] to melt at 144–145°. We prepared this latter material from the picrates of the individual compounds, and the product was identical in m.p. and mixed m.p. with material isolated above. Since the starting material for the lithium aluminum hydride reduction was free of 1-methylimidazole, this compound may have been formed by the action of the hydride on VI (R_2 = CH_3). Removal of an ester group by lithium aluminum hydride has been reported.[13] An alternative possibility would be the hydrolysis and decarboxylation of unreduced ester during water treatment of the reduction mixture or during subsequent treatment with picric acid. The yields of 1-methylimidazole and 1-methyl-2-hydroxymethylimidazole were 19 and 36%, respectively.

(12) R. Grindley and F. L. Pyman, *J. Chem. Soc.*, 3128 (1927).

(13) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

The 1-methyl-2-imidazolecarboxylic acid (III, R_1 = CH_3) was difficult to isolate because of its large solubility in polar solvents, its amphoteric nature and its ease of decarboxylation. Recrystallization of the acid from ethanol–water resulted in apparent decarboxylation, and attempts to prepare a picrate derivative only resulted in isolation of the picrate of 1-methylimidazole. In several reactions of 1-methyl-2-lithioimidazole, we were able to demonstrate better metalation yields than the 32% reported above for II. The carboxylic acid III (R_1 = CH_3) formed a bright blue, highly insoluble Cu(II) complex consisting of two molecules of the acid anion to one cupric ion. Using this complex to remove III after a metalation and carbonation indicated a 39% yield of III (R_1 = CH_3). The copper complex seems to chelate through the nitrogen atom in the 3-position, since 1-methyl-5-imidazolecarboxylic acid does not give the complex. Reaction of II (R_1 = CH_3) and benzophenone allowed isolation of 86% of the corresponding carbinol VII, and II with α-naphthyl isocyanate gave 66% of the corresponding amide.

1-Benzylimidazole was metalated with a slight excess of n-butyllithium and after carbonation a 67% yield of a monocarboxylic acid was obtained. This acid was indicated to be 1-benzyl-2-imidazolecarboxylic acid III (R_1 = $C_6H_5CH_2$—) through its m.p. of 104° (compared to a value of 106° given by Jones[14] for this compound) and its ready formation of a chelate with Cu(II) ion. This evidence does not exclude rigorously the possibility of metalation in the 4-position (the 4-acid is not known), but the earlier results with the 1-methylimidazole seemed to render this highly unlikely.

Metalation of 1-benzylimidazole followed by treatment with quinoline gave 1-benzyl-2-(2′-quinolyl)-imidazole (VIII) in low yield.

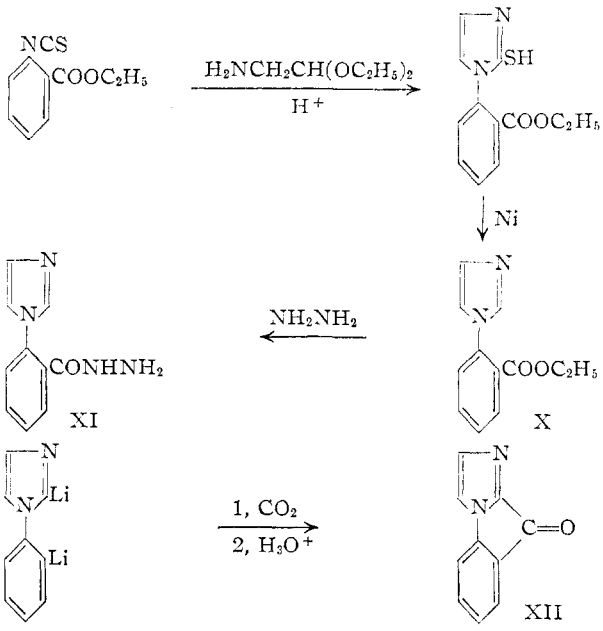
The metalation of 1-phenylimidazole with a slight excess of n-butyllithium occurred in 60% yield as indicated by carbonation and isolation of the carboxylic acid as the Cu(II) complex IV (R_1 = C_6H_5). The results on metalation of 1-methylimidazole and the formation of the copper complex indicated metalation in the 2-position of the imidazole ring. The 2′-position in the benzene ring was eliminated as a possible site of metalation by synthesis of the ethyl ester of 1-(*o*-carboxyphenyl)-imidazole (X) by the route shown in Scheme II. Comparison of X with the acid from metalation through the hydrazides V and XI indicated that the two were not identical. That the benzene ring can be involved in metalation was shown by the action of a threefold excess of n-butyllithium on 1-phenylimidazole. Carbonation gave in low yield 4-oxoimidazo[1,2-a]indoline (XII). The formation of cyclic ketones of this type from dimetalation and carbonation has been observed in the cases of 1-phenylpyrrole[15] and 1-phenylindole.[2] No dicarboxylic acid was isolated.

Reaction of 1-phenyl-2-lithioimidazole with phenyl isocyanate, benzophenone and ethyl chloroformate gave the expected products as indicated in Scheme I.

(14) R. G. Jones, *ibid.*, **71**, 383 (1949).

(15) D. A. Shirley, B. H. Gross and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

SCHEME II



Acknowledgment.—We should like to express appreciation to the Eli Lilly and Co. for financial support of this investigation and to Dr. Reuben G. Jones of that organization for samples of 1-benzyl-2-mercaptoimidazole and methyl 1-methyl-2-mercapto-5-imidazolecarboxylate.

Experimental[16]

1-Methylimidazole was prepared from imidazole[17] and methyl iodide by the procedure of Cowgill and Clark.[18]

1-Methyl-5-imidazolecarboxylic Acid.—1-Methylimidazole (17.9 g. or 0.218 mole) was added dropwise to a solution of *n*-butyllithium prepared from 34.2 g. (0.25 mole) of *n*-butyl bromide. The reaction period was 3 hr. at room temperature and 1 hr. at the reflux temperature of ether. The reaction mixture was carbonated by pouring it into a slurry of ether and crushed solid carbon dioxide and then hydrolyzing with 100 ml. of 50% ethanol. The solution was cooled to 5–10° and acidified. A white solid (1.5 g.) m.p. 135–235°, was collected by filtration and dried. After two recrystallizations from ethanol–water mixtures, 0.4 g. (1.5%) of solid remained, m.p. 275–277° dec.

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.48, 47.50; H, 4.86, 4.74; N, 22.13, 22.10.

A picrate of the acid melted at 198–201°. Hubball and Pyman[11] report the picrate of 1-methyl-5-imidazolecarboxylic acid to melt at 198–199°.

Anal. Calcd. for $C_{11}H_9N_5O_9$: N, 19.72. Found: N, 19.74.

The methyl ester of the acid was prepared by treatment with diazomethane. The melting point of the ester (39–40°) could not be raised to the literature value of 68–70°.[11] **A picrate** derivative of the ester melted at 169–171°. Hubball and Pyman[11] report the picrate of methyl 1-methyl-5-imidazolecarboxylate to melt at 171°.

Anal. Calcd. for $C_{12}H_{11}N_5O_7$: C, 39.03; H, 3.00; N, 18.97. Found: C, 38.90, 39.01; H, 3.15, 2.95; N, 19.10, 19.07.

A mixed melting point of this picrate derivative with the picrate derivative of an authentic sample of methyl 1-methyl-5-imidazolecarboxylate showed no depression. The authentic sample was prepared by the nitric acid oxidation of methyl 1-methyl-2-mercapto-5-imidazolecarboxylate according to the procedure of Jones.[19]

Mixed Hydrobromide and Hydrochloride Salt of 1-Methyl-2-imidazolecarboxylic Acid.—The acid filtrate from the above metalation was made basic with solid sodium carbonate and sodium hydroxide. The lithium carbonate which precipitated was removed by filtration and, after first extracting with benzene, the basic solution was concentrated nearly to dryness and acidified with sulfuric acid. The acid solution was allowed to evaporate to dryness at room temperature. The resulting solid was extracted several times with absolute ethanol. On addition of ether to the ethanol extracts white solid formed, and in this manner 13.5 g. (32%) of solid, m.p. 119° dec., was obtained. A potentiometric titration of the solid with base showed two breaks in the curve and the neutralization equivalent found for the product was 94. The solid gave a negative test for sulfate ion and a positive test for both bromide and chloride ion.

Anal. Calcd. for $C_5H_7ClN_2O_2$ (hydrochloride): C, 36.97; H, 4.32; N, 17.2; neut. equiv., 81. Calcd. for $C_5H_7BrN_2O_2$ (hydrobromide): C, 29.00; H, 3.41; N, 11.5; neut. equiv., 104. Calcd. for equimolar mixture of hydrobromide and hydrochloride: C, 32.98; H, 3.86; N, 14.35; neut. equiv., 92. Found: C, 32.08; H, 3.85; N, 14.41; neut. equiv., 94.

1-Methyl-2-imidazolecarboxylic Acid Hydrobromide.—The mixed acid salt (1 g.) was dissolved in 2.5 ml. of water and hydrogen bromide gas passed over the solution (maintained at 0°) for 1 hr. The solid which slowly precipitated was removed by filtration and washed with a small amount of cold ethanol. The dried solid melted at 126.5° dec.

Anal. Calcd. for $C_5H_7BrN_2O_2$: C, 29.00; H, 3.41; Br, 38.59. Found: C, 29.42, 29.20; H, 3.54, 3.39; Br, 39.19, 38.42.

Methyl 1-Methyl-2-imidazolecarboxylate Picrate.—The mixed acid salt from the above metalation (1 g.) in 15 ml. of distilled water was passed through 2 g. of Amberlite 120 (strong cation exchanger) and then through 2 g. of IRA 400 (strong anion exchanger). After evaporation of the water, the solid residue was treated with an ethereal solution of diazomethane. The excess diazomethane was expelled on the water-bath and the ether solution filtered from solid material which was present. A saturated solution of picric acid in ethanol was added to the filtrate, and the picrate derivative which formed was recrystallized from ethanol. It melted at 143–145°. The yield was low.

Anal. Calcd. for $C_{12}H_{11}N_5O_9$: C, 39.03; H, 3.00; N, 18.97. Found: C, 39.10, 39.12; H, 3.09, 3.01; N, 18.86, 18.98.

1-Methyl-2-imidazolecarboxylic Acid.—To 1-methylimidazole (10.9 g. or 0.135 mole) in 100 ml. of dry ether cooled in an acetone–solid carbon dioxide-bath was added 100 ml. of a *n*-butyllithium solution prepared from 0.2 mole of *n*-butyl chloride. The reaction mixture was stirred for 2 hr. at −60°, 3 hr. at room temperature and then carbonated in the usual manner. Water (30 ml.) was added and the combined ether and aqueous layers maintained at 0° were acidified with hydrochloric acid to *p*H 2–4. The ether was rapidly evaporated by a current of air and the white solid (2.85 g.) which slowly formed was removed by filtration. It melted at 119° dec. A sample for analysis was recrystallized below room temperature from a mixture of water and acetone. The melting point was raised to 121.5° dec. Analysis indicated the acid was a monohydrate.

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.66; H, 5.59; N, 19.4; H_2O, 12.50; neut. equiv., 144. Found: C, 41.79; H, 5.67; N, 19.6; H_2O, 12.52; neut. equiv., 139.

The filtrate from the above was made basic, and 1.7 g. of 1-methylimidazole was recovered by a continuous ether extraction for 96 hr. The alkaline solution was evaporated to dryness *in vacuo* and the solid residue extracted with absolute ethanol in a Soxhlet extractor. The ethanol was evaporated and the residue dissolved in 10 ml. of water. The solution was cooled to 0° and acidified with hydrochloric acid to *p*H 2–4. Solid slowly formed (1.5 g.). This was recrystallized from aqueous acetone yielding an additional

(16) Microanalyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Weiler and Strauss, Oxford, England. All melting points are uncorrected.

(17) H. R. Snyder, R. G. Handrick and L. A. Brooks, *Org. Syntheses*, **22**, 65 (1942).

(18) R. W. Cowgill and W. M. Clark, *J. Biol. Chem.*, **198**, 33 (1952).

(19) R. G. Jones, THIS JOURNAL, **71**, 644 (1949).

1.1 g. of 1-methyl-2-imidazolecarboxylic acid monohydrate, m.p. 120° dec.

The total yield of product was 3.95 g. or 20%. None of the 5-acid was obtained.

Treatment of 0.74 g. (0.0052 mole) of this acid with an ethereal diazomethane solution, followed by alcoholic picric acid solution as in the above procedure, yielded 0.42 g. or 22% of a picrate derivative, m.p. 143–144°. A mixed melting point with the picrate derivative of the methyl ester prepared from the mixed hydrobromide, hydrochloride salt of 1-methyl-2-imidazolecarboxylic acid showed no depression.

Ethyl 1-Methyl-2-imidazolecarboxylate.—The yellow ethereal solution from the metalation of 11.0 g. (0.134 mole) of 1-methylimidazole with *n*-butyllithium, prepared from 20.5 g. (0.15 mole) of *n*-butyl bromide and 3.0 g. of lithium, was decanted from solid material present and added dropwise to a solution of 34.0 g. (0.3 mole) of ethyl chloroformate in dry ether maintained at −60°. The solid from the metalation reaction was washed with three 30-ml. portions of ether and the wash solutions added to the reaction mixture. The remaining solid was dissolved in water, the solution saturated with potassium carbonate, extracted with ether and the ether solution treated with a saturated alcohol solution of picric acid. In this way, 2.0 g. of 1-methylimidazole was recovered as the picrate, m.p. 158–159°. The above reaction mixture was stirred for 7 hr. at −60° and allowed to warm to room temperature. A pink solid (20 g.), probably a quaternary ammonium salt of ethyl chloroformate and ethyl 1-methyl-2-imidazolecarboxylate, was separated by filtration. The solid was a strong lachrymator and slowly evolved a gas on standing. The ester was obtained by dissolving the solid in water, adding a saturated solution of sodium carbonate and extracting with chloroform. The residue from the chloroform was vacuum distilled twice to yield 1.7 g. of product, b.p. 55° (0.3 mm.). The yield was 10%.

A picrate derivative of the ester melted at 121° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{13}H_{13}N_5O_9$: C, 40.74; H, 3.42; N, 18.27. Found: C, 40.90; H, 3.43; N, 18.49.

The hydrazide, m.p. 109–110°, was prepared in 60% yield from the ethyl ester using the procedure of Jones and McLaughlin.[20]

Anal. Calcd. for $C_5H_8N_4O$: N, 39.88. Found: N, 40.13.

This hydrazide was identical with one prepared from 1-methyl-2-imidazolecarboxylic acid by treatment with diazomethane followed by hydrazine hydrate.

1-Methyl-2-hydroxymethylimidazole.—Ethyl 1-methyl-2-imidazolecarboxylate (0.9 g.) was added dropwise to a stirred solution of 1.5 g. of lithium aluminum hydride in 40 ml. of dry ether. An additional 0.5 g. of lithium aluminum hydride was added and stirring continued for 1 hr. The mixture was hydrolyzed with wet ether followed by a small amount of water. The solid was removed by filtration and the ether filtrate was added to a solution of 3 g. of picric acid in 15 ml. of ethanol. The solid on the filter pad was washed with methanol saturated with carbon dioxide and then with chloroform. The wash solutions also were added to the picric acid solution. The first fraction of picrate, 0.65 g., melted at 145–146° after recrystallization from water. Grindley and Pyman[12] report the molecular compound of the picrates of 1-methylimidazole and 1-methyl-2-hydroxymethylimidazole to melt 144–145°.

Anal. Calcd. for $C_{21}H_{20}N_{10}O_{15}$: C, 38.65; H, 3.07; N, 21.5. Found: C, 38.72; H, 2.93; N, 21.2.

A second and third fraction of picrate with a combined weight of 0.47 g. was obtained by concentrating the filtrate from the first fraction. The melting point after recrystallization from water was 139–140°. Grindley and Pyman[12] report the picrate of 1-methyl-2-hydroxymethylimidazole to melt at 138°.

Anal. Calcd. for $C_{11}H_{11}N_5O_8$: C, 38.71; H, 3.25; N, 20.53. Found: C, 38.50; H, 3.22; N, 20.5.

The picrate of 1-methylimidazole (0.05 g.) was dissolved in an aqueous solution containing 0.05 g. of the lower melting picrate from above. The solid which precipitated lost water at 100° and then remelted from 145 to 146.5°. Pyman[12] reports that the air-dried molecular compound is a hemi-hydrate. After a recrystallization from water followed by drying, this picrate melted at 145.5–146.5° and gave no depression in m.p. when mixed with the first picrate fraction above.

Copper(II) Complex of 1-Methyl-2-imidazolecarboxylic Acid.—To 1-methylimidazole (2 g. or 0.0245 mole) in 45 ml. of dry ether was added 0.033 mole of *n*-butyllithium in 30 ml. of dry ether. The reaction mixture was stirred for 1 hr. and then carbonated in the usual manner. The carbonation mixture was hydrolyzed with 40 ml. of water and the solution made slightly acid with concentrated hydrochloric acid. After the ether had evaporated, copper sulfate (3.5 g.) in 50 ml. of water was added. It was necessary to add a few drops of hydrochloric acid before precipitation of the copper complex occurred. A deep blue finely divided precipitate formed which after careful washing and drying weighed 1.5 g. (39%).

Anal. Calcd. for $C_{10}H_{10}CuN_4O_4$: C, 38.27; H, 3.21. Found: C, 37.74, 37.73; H, 3.23, 3.38.

The best results in the metalation of 1-methylimidazole and other N-substituted imidazoles were obtained by preparing the *n*-butyllithium solution in advance, storing it in a stoppered separatory funnel under an atmosphere of nitrogen at 15° or below until the sludge from the preparation had settled out and then pipetting out the required amount of clear supernatant solution for the metalation reactions. This procedure was employed in this and the following experiments.

1-Methyl-2-imidazolyldiphenylcarbinol (VII).—To 1-methylimidazole (1.0 g. or 0.012 mole) in 45 ml. of ether was added from a pipet 0.0165 mole of *n*-butyllithium in 15 ml. of ether. After a 1-hr. reaction period, solid benzophenone (2.36 g. or 0.013 mole) was added with stirring to the green reaction mixture. After 4.5 hr. at room temperature, the reaction mixture was hydrolyzed and then made acid with dilute hydrochloric acid. The aqueous layer was separated and made alkaline. The white solid which formed was filtered from the basic solution, washed with water and dried yielding 2.8 g. (86%) of white crystals, m.p. 190–192°. A sample, m.p. 192–193°, for analysis was recrystallized from water–ethanol mixture.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.06, 77.09; H, 6.33, 6.10; N, 10.50.

N-α-Naphthyl-1-methyl-2-imidazolecarboxamide.—To a solution of 1-methyl-2-lithioimidazole, prepared from 2.85 g. (0.035 mole) of 1-methylimidazole in 45 ml. of dry ether, was added 6.0 g. (0.035 mole) of α-naphthyl isocyanate dissolved in 25 ml. of dry ether. The resulting mixture was stirred and heated under reflux for 5 hr. Absolute ethanol (15 ml.) was added and the mixture stirred for 20 minutes, after which it was poured into 100 ml. of cold water. The ether was allowed to evaporate and the heavy white precipitate which formed in the remaining aqueous layer was collected by filtration. The product was dissolved in a mixture of acetone, ethanol and ether and a small amount of N,N′-di-α-naphthylurea, m.p. 297–298°, was removed by filtration. The filtrate was concentrated and the solid residue was extracted with a 10% hydrochloric acid solution. The acid solution was made basic, and the solid product which formed was collected by filtration, washed with water and then recrystallized from an acetone–water mixture yielding 5.8 g. (66%) of amide, m.p. 125.5–127°.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.70, 71.65; H, 5.40, 5.39; N, 16.40, 16.25.

1-Benzylimidazole.—1-Benzylimidazole was prepared by the nitric acid oxidation of 1-benzyl-2-mercaptoimidazole in 80% yield according to the method of Jones.[14] The 1-benzyl-2-mercaptoimidazole was supplied by Dr. R. G. Jones.

1-Benzyl-2-imidazolecarboxylic Acid.—A slight excess of the calculated amount of *n*-butyllithium in ether was added dropwise to a stirred solution of 5 g. (0.032 mole) of 1-benzylimidazole in 20 ml. of dry ether maintained at −60° in an acetone–solid carbon dioxide-bath. The reaction mixture was maintained at −60° for 2 hr. and then the cold bath was removed and stirring continued for another 2.5 hr. The reaction mixture was carbonated in the usual manner, hydrolyzed with 50 ml. of water and the ether allowed to evaporate. On acidification there was obtained

(20) R. G. Jones and K. C. McLaughlin, THIS JOURNAL, **71**, 2444 (1949).

4.27 g. (67%) of product which melted with decomposition at 103–104°. Jones[14] gives 106° dec. as the melting point of 1-benzyl-2-imidazolecarboxylic acid. A sample was recrystallized from water and melted at 104° dec. The filtrate was made basic and extracted with chloroform for the recovery of 0.81 g. of 1-benzylimidazole. The yield of acid based on 4.19 g. of 1-benzylimidazole was 80%.

A copper(II) complex of 1-benzyl-2-imidazolecarboxylic acid was prepared.

Anal. Calcd. for $C_{22}H_{18}CuN_4O_4$: N, 12.03. Found: N, 12.37.

1-Benzyl-2-imidazolecarboxamide.—1-Benzyl-2-imidazolecarboxylic acid was converted[21] into the amide, m.p. 151–152.5°. Recrystallization was from benzene.

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.9. Found: C, 63.7; H, 5.60; N, 20.6, 20.5.

1-Benzyl-2-(2'-quinolyl)-imidazole (VIII).—A solution of 1.03 g. (0.008 mole) of quinoline in 20 ml. of ether was added to a solution of 1-benzyl-2-lithioimididazole, prepared from 1.17 g. (0.0074 mole) of 1-benzylimidazole in 75 ml. of ether. The solution was refluxed and stirred for 1 hr., cooled and hydrolyzed with 20 ml. of water. Nitrobenzene (1 ml.) was added to oxidize the intermediate dihydro compound and the mixture stirred and refluxed for 30 minutes. The ether layer was separated and dried over magnesium sulfate. The ether was evaporated and the red, oily residue was extracted with a 5% hydrochloric acid solution. The aqueous acid solution was neutralized to precipitate an oil. Crystallization was induced by rubbing the oil in petroleum ether (b.p. 35–60°) yielding 0.61 g. (29%) of crude product melting 93–100°. A sample for analysis was treated with charcoal in ethanol and then recrystallized from an ethanol–water mixture. The product was a white crystalline solid, m.p. 114.5–115.5°.

Anal. Calcd. for $C_{19}H_{15}N_3$: N, 14.7. Found: N, 14.7.

A picrate derivative, m.p. 200–201°, was prepared.

Anal. Calcd. for $C_{25}H_{18}N_6O_7$: N, 16.3. Found: N, 16.0, 16.1.

1-Phenyl-2-mercaptoimidazole.—1-Phenyl-2-mercaptoimidazole was prepared by the method of Wohl and Marckwald[22] in 85% yield from phenyl isothiocyanate and aminoacetal.

1-Phenylimidazole.—1-Phenylimidazole was prepared in 66% yield from the nitric acid oxidation of 1-phenyl-2-mercaptoimidazole according to the procedure of Jones[14] for the oxidation of 1-benzyl-2-mercaptoimidazole. The product was distilled under vacuum and the boiling point was 118° at 2 mm. The picrate derivative melted at 155–156°, which corresponds to the literature value for the picrate of 1-phenylimidazole.[23]

Copper(II) Complex of 1-Phenyl-2-imidazolecarboxylic Acid.—A slight excess of the calculated amount of *n*-butyllithium was added from a pipet to a solution of 5.0 g. (0.035 mole) of 1-phenylimidazole in 30 ml. of ether. The resulting mixture was stirred for 8 hr. and then carbonated in the usual manner. The carbonation mixture was hydrolyzed with 80 ml. of water and the yellow ether layer was separated. The aqueous layer was acidified to the neutral point. Since the expected acid failed to precipitate a concentrated aqueous solution of copper sulfate was added and a pale blue water-insoluble precipitate formed which after careful washing and drying weighed 3.5 g. (46%).

Anal. Calcd. for $C_{20}H_{14}CuN_4O_4$: C, 54.85; H, 3.22; N, 12.8. Found: C, 54.60, 54.64; H, 3.07, 3.17; N, 12.8, 12.8.

On treatment of the ether layer residue from the metalation with alcoholic picric acid solution, 2.85 g. of the picrate of 1-phenylimidazole, m.p. 155°, formed. This corresponds to 1.0 g. of 1-phenylimidazole. The yield of the copper complex based on 4 g. of 1-phenylimidazole was 60%.

1-Phenyl-2-imidazolecarboxylic Acid Hydrazide.—To a solution of 2.9 g. (0.02 mole) of 1-phenylimidazole in dry ether was added 0.025 mole of *n*-butyllithium in 30 ml. of dry ether. The resulting solution was stirred for 1 hr., and ethyl chloroformate (9.5 g.) in 10 ml. of dry ether was added rapidly with cooling of the reaction vessel in an acetone–solid carbon dioxide-bath. Stirring was continued overnight and the reaction was hydrolyzed with water (25 ml.). Solid potassium carbonate was added in excess and stirring was continued for several hours. The ether layer was separated and the ether allowed to evaporate. The oily residue was heated with 6 ml. of hydrazine hydrate (99–100%) and 5 ml. of ethanol for 3 hr. on the steam-bath. White needles formed upon cooling the solution. These were collected by filtration and recrystallized from absolute ethanol, yielding 0.82 g. (20%) of the hydrazide of 1-phenyl-2-imidazolecarboxylic acid, m.p. 211–212°.

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.37; H, 4.76; N, 27.80.

Ethyl 1-Phenyl-2-imidazolecarboxylate.—1-Phenyl-2-lithioimidazole, prepared from 2 g. (0.014 mole) of 1-phenylimidazole, was allowed to react with excess ethyl chloroformate. The resulting ester was purified by treatment with charcoal in aqueous alcohol solution followed by recrystallization from a dry ether–ligroin (b.p. 35–60°) mixture to yield 0.14 g. (5%) of product, m.p. 94–94.5°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.70; H, 5.63; N, 13.10.

A picrate derivative melted at 182.5–186°.

Anal. Calcd. for $C_{18}H_{15}N_5O_9$: N, 15.73. Found: N, 16.00, 16.10.

1-Phenyl-2-imidazoyldiphenylcarbinol.—To a solution of 1-phenyl-2-lithioimidazole, prepared from 2 g. (0.014 mole) of 1-phenylimidazole in 25 ml. of dry ether, was added 2.55 g. (0.015 mole) of benzophenone. The mixture was stirred for 15 minutes and then hydrolyzed with 25 ml. of water. The ether layer was separated and the ether allowed to evaporate. The residue was recrystallized once from ethanol yielding 3.6 g. (76%) of white crystalline solid melting at 71.5–76.5°. Recrystallization failed to improve the melting point and analysis indicated the product to be a monohydrate.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.5; H, 6.06; N, 8.30.

The hydrochloride of 1-phenyl-2-imidazoyldiphenylcarbinol melted at 179–181°.

Anal. Calcd. for $C_{22}H_{19}ClN_2O$: Cl, 9.79. Found: Cl, 9.99.

N-Phenyl-1-phenyl-2-imidazolecarboxamide.—To a solution of 1-phenyl-2-lithioimidazole, prepared from 1.96 g. (0.014 mole) of 1-phenylimidazole in 75 ml. of dry ether, was added 2 ml. of freshly distilled phenyl isocyanate in 25 ml. of dry ether. The resulting solution was refluxed and stirred for 1 hr. Absolute ethanol (25 ml.) was added and the mixture stirred at room temperature overnight. The brown reaction mixture was poured into 100 ml. of ice-water and the ether layer was separated. The aqueous layer was extracted once with ether and the ether evaporated from the combined ether layers. The residue was recrystallized three times from dilute ethanol using a charcoal treatment on the last recrystallization. There was obtained 1.4 g. (39%) of amide, m.p. 99–100°. An additional 0.6 g. of product was obtained by concentration of the filtrate.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98; N, 15.96. Found: C, 72.62; H, 5.20; N, 16.20.

Dimetalation of 1-Phenylimidazole.—To 2.4 g. (0.017 mole) of 1-phenylimidazole in ether was added an ether solution of 0.045 mole of *n*-butyllithium. The resulting solution was refluxed for 12 hr. and the green reaction mixture then carbonated in the usual manner. Following hydrolysis with 25 ml. of water, 15 ml. of a 10% solution of hydrochloric acid was added and the bright yellow ether layer was separated from the brown aqueous layer. The ether layer was evaporated and the bright yellow crystalline residue weighed 0.13 g. after recrystallization from acetone, corresponding to a 5% conversion to 4-oxoimidazo[1,2-a] indoline (XII). A sample sublimed for analysis melted at 162–163°.

Anal. Calcd. for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.28; H, 3.45; N, 16.60.

On acidification of the aqueous layer a small amount of yellow solid formed from which no pure acid could be obtained.

(21) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 157.

(22) A. Wohl and W. Marckwald, *Ber.*, **22**, 568, 1354 (1889).

(23) R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 397 (1930).

1-(*o*-Carbethoxyphenyl)-2-mercaptoimidazole.—1-(*o*-Carbethoxyphenyl)-2-mercaptoimidazole was prepared by condensation of *o*-carbethoxyphenyl isothiocyanate with aminoacetal in the presence of acid according to the method of Wohl and Marckwald[22] for the preparation of 1-aryl- or 1-alkylimidazole-2-thiols. The *o*-carbethoxyphenyl isothiocyanate was prepared according to the procedure of Dyson and George[24] by the condensation of thiophosgene with aromatic primary amines. The over-all yield of the product, m.p. 123–124.5°, was 23%.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.29. Found: C, 58.15, 58.03; H, 4.93, 4.71; N, 11.00, 11.20.

Hydrazide of 1-(*o*-Carboxyphenyl)-imidazole (XI).—1-(*o*-Carbethoxyphenyl)-2-mercaptoimidazole (0.9 g. or 0.0036 mole) was heated to reflux in 45 ml. of ethanol with excess Raney nickel for 45 minutes according to the procedure of Cook, Downer and Heilbron[25] for the desulfurization of 5-amino-2-mercapto-1-methylimidazole. The Raney nickel was removed by filtration and the ethanol filtrate evaporated on the water-bath. The oily residue was heated on the steam-bath with 4 ml. of 99–100% hydrazine hydrate and 3 ml. of ethanol for 3 hr. After adding 3 ml. of water to the solution, the ethanol was removed *in vacuo* and white solid slowly formed. It was collected by filtration and recrystallized from ethanol yielding 0.10 g. (14%) of product, m.p. 209–210°.

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.45, 59.45; H, 4.47, 4.43; N, 27.6, 27.8.

A mixture of this product with the hydrazide prepared from ethyl 1-phenyl-2-imidazolecarboxylate, m.p. 210–211°, melted in the range 179 to 190°.

(24) G. M. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924).

(25) A. H. Cook, J. D. Downer and I. Heilbron, *ibid.*, 2028 (1948)

KNOXVILLE, TENNESSEE

[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

The Effect of Structure on Kinetics and Mechanism of the Alkaline Hydrolysis of Anilides[1]

BY SYDNEY S. BIECHLER[2] AND ROBERT W. TAFT, JR.

RECEIVED APRIL 8, 1957

The rates of aqueous alkaline hydrolysis of trifluoroacetanilide and a series of N-methylanilides, $ROCN(CH_3)C_6H_5$, have been determined at 25.5° spectrophotometrically. The reactions have been carried out with large excesses of hydroxide ion, and pseudo first-order kinetics are obtained. The rate law followed by trifluoroacetanilide is $k_1 = k_3(OH^-)/1 + (OH^-)K$ and by the N-methylanilides is $k_1 = k_2(OH^-) + k_3(OH^-)^2$. The observed rate equations are explained in terms of a reaction sequence involving two reactive intermediates and the reversible formation of the conjugate base of trifluoroacetanilide as an unreactive side product. The divalent anion intermediate which leads to third-order kinetics is an analog of the intermediates proposed for the aqueous alkaline cleavage of acetylacetone and for the Cannizzaro reaction. The ratio of third to second-order constants, k_3/k_2, for the N-methylanilides increases with increasing electron-withdrawal and decreasing steric requirements of the substituent, R, as shown by the correlation equation: $\log (k_3/k_2) = \sigma^*\rho^* + \delta E_s +$ const. Contribution of two types of steric effects to the rate is indicated, one of which closely parallels steric effects in ester hydrolysis rates. It is suggested that the second steric component results from an inhibition of resonance in the anilide. The second-order hydrolysis constant for trifluoro-N-methylacetanilide is twenty-five times greater than that of trifluoroacetanilide in accord with this proposal.

The kinetics of the alkaline saponification of esters has been extensively investigated, but relatively little work has been done on the kinetics of the alkaline hydrolysis of amides and anilides.

Meloche and Laidler have studied *p*-substituted benzamides[3]; Cason and co-workers, several branched-chain amides[4]; Bruylants and co-workers, straight-chain aliphatic amides.[5] The alkaline alcoholysis of phenyl-substituted acetanilides has been studied by Verkade, Wepster and co-workers.[6] Oxygen exchange in the alkaline hydrolysis of benzamide has been investigated by Bender and co-workers.[7] All of these investigators carried out the hydrolysis rates using equivalent concentrations of base and of amide, with the exception of Wepster, *et al.*, who employed an excess of base. Satisfactory fit to a rate equation first order in amide and in hydroxide ion was reported in each case. These results are analogous to the kinetics obtained for the alkaline saponification of normal esters.

The present investigation was undertaken to determine the effect of structure in the acyl component of an amide on its hydrolysis rate. It was further desired to attempt a quantitative separation of the observed effects on the free energy of activation to contributing polar, steric and resonance effects and, in turn, correlation of these effects with corresponding ones from other reactions. Taft has carried out this kind of analysis for the effects of structure on the rates of alkaline saponification of esters.[8]

While Laidler and Meloche have carried out limited work of this general nature in the aromatic series, the data available in the aliphatic series do not include nearly enough variation of structure to permit conclusions of a quantitative nature.

(1) This work was supported in part by the Office of Naval Research, Project NRO55-328. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) (a) Taken from the Ph.D. Thesis of Sydney S. Biechler, The Pennsylvania State University, August, 1956; (b) Shell Oil Co. Fellow for 1955–1956.

(3) I. Meloche and K. J. Laidler, THIS JOURNAL, **73**, 1712 (1951).

(4) (a) J. Cason, C. Gastaldo, D. L. Glusker, J. Allinger and L. B. Ash, *J. Org. Chem.*, **18**, 1129 (1953); (b) J. Cason and H. Wolfhagen, *ibid.*, **14**, 155 (1949).

(5) (a) Mlle. De Roo and A. Bruylants, *Bull. soc. chim. Belges*, **63**, 140 (1954); (b) M. Willems and A. Bruylants, *ibid.*, **60**, 191 (1951).

(6) (a) P. E. Verkade and P. H. Witjens, *Rec. trav. chim.*, **62**, 201 (1943); (b) B. M. Wepster and P. E. Verkade, *ibid.*, **67**, 411, 425 (1948); **68**, 77, 88 (1949); **69**, 1393 (1950); (c) H. J. Biekart, H. B. Dessens, P. E. Verkade and B. M. Wepster, *ibid.*, **71**, 1245 (1952).

(7) (a) M. L. Bender and R. D. Ginger, THIS JOURNAL, **77**, 348 (1955); (b) M. L. Bender, R. D. Ginger and K. G. Kemp, *ibid.*, **76**, 3350 (1954); (c) for spectral evidence supporting the formation of intermediate II, *cf.* M. L. Bender, *ibid.*, **75**, 5986 (1953).

(8) R. W. Taft, Jr., *ibid.*, **74**, 3120 (1952); **75**, 4231 (1953); *cf.* Chapt. 13, in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956.