When *N*-(2-hydroxyethyl)benzamides (I) were treated with phosphorus pentachloride, stable *N*-(2-chloroethyl)benzimidyl chlorides (II) were produced which reacted readily with various secondary amines to give good yields of *N'*-(2-chloroethyl)-*N,N*-dialkylbenzamidines (III). At elevated temperatures in a high-boiling solvent or an autoclave, either the remaining alkyl halogen of III was replaced to give the desired *N,N*-dialkyl-*N'*-(2-dialkylaminoethyl)benzamidines (IV), or both halogens of II were replaced simultaneously to give other *N,N*-dialkyl-*N'*-(2-dialkylaminoethyl)benzamidines (V). We were thus able to control the placement of NRR groups in the tertiary benzamidines which are listed in Table I.

EXPERIMENTAL[3]

The following examples illustrate the general procedures used for preparation of the compounds listed in Table I.

N-(2-Chloroethyl)benzimidyl chloride. To a vigorously stirred solution of 33.0 g. (0.2 mole) of *N*-(2-hydroxyethyl)-benzamide[4] in 500 ml. of boiling benzene was added 83.3 g. (0.4 mole) of phosphorus pentachloride in small portions. With each addition a vigorous reaction ensued, and hydrogen chloride was evolved. As the reaction progressed, a heavy white crystalline precipitate separated. During a period of 3 hr. of stirring and refluxing the solid dissolved. Benzene and phosphorus oxychloride were removed by warming *in vacuo*, and the residual pale green oil was distilled through a 6-in. Vigreux column. Occasionally, a portion of phosphorus pentachloride preceded the distillate which made it necessary to disassemble the apparatus and wash out the solid collected on the walls of the condenser. Distillation was then continued to give 30.6 g. of *N*-(2-chloroethyl)benzimidyl chloride (compound No. 1, Table I) as a colorless oil.

N'-(2-Chloroethyl)-N,N-diethylbenzamidine. A solution of 20.2 g. (0.1 mole) of *N*-(2-chloroethyl)benzimidyl chloride in 150 ml. of benzene was mixed with 14.6 g. (0.2 mole) of diethylamine, and refluxed for 2 hr. The mixture was cooled, and the diethylamine hydrochloride collected by filtration. It weighed 10 g. (92% yield). The filtrate was washed with two 300-ml. portions of water and was then concentrated by warming *in vacuo* to a red oily residue. The oil was distilled to give 14.6 g. of *N'*-(2-chloroethyl)-*N,N*-diethylbenzamidine (compound No. 2, Table I).

N,N-Diethyl-N'-[2-(1-piperidyl)ethyl]benzamidine. A mixture of 16.7 g. (0.07 mole) of *N'*-(2-chloroethyl-*N,N*-diethylbenzamidine, 29.9 g. (0.35 mole) of piperidine, and 100 ml. of toluene was refluxed for 24 hr. The precipitated piperidine hydrochloride was collected by filtration (7 g., 83% yield). Toluene was removed from the filtrate by warming *in vacuo*, and the residual yellow oil was distilled to furnish 8.7 g. of *N,N*-diethyl-*N'*-[2-(1-piperidyl)ethyl]-benzamidine as a colorless oil (compound No. 3, Table I).

N,N-Pentamethylene-N'-[2-(1-piperidyl)ethyl]benzamidine. *N*-(2-Chloroethyl)benzimidyl chloride (32.4 g., 0.16 mole) dissolved in 500 ml. of toluene was stirred and mixed with 68.1 g. (0.8 mole) of piperidine. The solution became warm and piperidine hydrochloride separated. The mixture was then heated at reflux for 16 hr. From the chilled mixture 35 g. (90% yield) of piperidine hydrochloride was collected by filtration. The filtrate was extracted with two 300-ml. portions of water, dried over Drierite, and the toluene removed by heating *in vacuo*. Upon distillation of the red oily residue there was obtained 32 g. of *N,N*-pentamethylene-*N'*-[2-(1-piperidyl)ethyl]benzamidine (compound No. 13, Table I) as a yellow oil.

The *dihydrochloride salts* were obtained by treating the benzamidine bases in absolute ether with an excess of ethereal hydrogen chloride. *Quaternization* was carried out by treating the bases in acetone at room temperature with a 2:1 ratio of methyl iodide to benzamidine base. Under these conditions, with the exception of *N,N*-diethyl-*N'*-[2-[1-piperidyl)ethyl]benzamidine dimethiodide (compound No. 19, Table I), only the monomethiodides were produced.

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(3) Analyses were carried out in the Institute's microanalytical laboratory by Mr. K. D. Fleischer and staff.

(4) Phillips and Baltzly, *J. Am. Chem. Soc.*, **69**, 200–204 (1947).

Further Studies in the Synthesis of Long-Chain Hydroxy Acids[1]

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Received June 6, 1961

In a previous paper,[3] the authors reported the preparation of four long-chain hydroxy acids by Raney nickel-catalyzed reduction and desulfurization of selected acidic derivatives of thiophene.

References concerning the development of the desulfurization reaction and its application to the synthesis of various classes of long-chain compounds may be found in the original article.[3] In addition to these previously cited references, the work of Gol'dfarb and co-workers[4–7] should be mentioned.

The work reported in our original article has now been extended to the preparation of four more long-chain hydroxy acids. All acids prepared in this extension were 10-hydroxy acids.

The initial work was undertaken to investigate the application of the desulfurization reaction to the preparation of hydroxy acids, as the older methods of synthesis, based on reduction of keto

(1) Presented in part before the 139th meeting of the American Chemical Society in St. Louis, Mo., March 1961.

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(3) K. E. Miller, C. Haymaker, and H. Gilman, *J. Org. Chem.*, **24**, 622 (1959).

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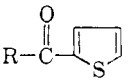
(5) Ya. L. Gol'dfarb and M. L. Kirmalova, *J. Gen. Chem. U.S.S.R.*, **26**, 3797 (1956); *Chem. Abstr.*, **52**, 14582g (1958).

(6) Ya. L. Gol'dfarb and P. A. Konstantinov, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 229 (1957); *Chem. Abstr.*, **52**, 15497h (1958).

(7) Ya. L. Gol'dfarb and P. A. Konstantinov, *Izvest. Akad. Nauk U.S.S.R., Otdel. Khim. Nauk*, 121 (1959); *Chem. Abstr.*, **53**, 16103a (1959).

TABLE I

n-ALKYL 2-THIENYL KETONES



Acyl Chloride	R(*n*-)	Yield, %	B.P.	M.P.	Sulfur, % Calcd.	Sulfur, % Found
Octanoyl	C_7H_{15}	89.5	150–154 (2.5)		15.24	15.18
Decanoyl	C_9H_{19}	92.7	174–177 (7)			
Tetradecanoyl	$C_{13}H_{27}$	68.0		33.5–34.5[a]	10.87	10.69
Hexadecanoyl	$C_{15}H_{31}$	81.6		42.0–43.0[a]	9.94	10.12

[a] Recrystallized from methanol.

acids or hydrolysis of halogenated acids, were quite limited. This limitation was due principally to the relative unavailability of the starting materials.

Since the appearance of the original paper[3] by the present authors, the preparation of a number of oxo- and hydroxy- acids has been reported.[8]

The synthesis of the hydroxy acids described in this paper involved six main steps.[3]

The position of the hydroxyl group is determined by the chain length of the ester acid chloride used. Thus, the use of 9-carbethoxynonanoyl chloride yields an acid with the hydroxyl group on the tenth carbon atom. The over-all chain length of the product, however, is dependent upon both the acyl chloride and the ester acid chloride used, remembering that of the total number of carbon atoms, four are furnished by the thiophene nucleus.

EXPERIMENTAL[9]

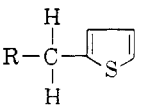
Acyl and ester-acid chlorides. These were prepared by the action of thionyl chloride on carboxylic acids and ethyl hydrogen sebacate, respectively. Benzene was employed as a solvent in the case of the carboxylic acids. The general procedure followed was that described in *Organic Syntheses*.[10,11] All products were purified by vacuum distillation.

n-Alkyl 2-thienyl ketones. A mixture of 0.15 mole of acyl chloride, 12.5 g. of thiophene, and 125 ml. of anhydrous thiophene-free benzene was cooled to −5°, and 16.5 g. of anhydrous stannic chloride was added dropwise, with stirring, during 30–45 min. The ice bath was then removed and the mixture was stirred for an additional 4 hr. Decomposition of the reaction mixture was accomplished by the addition of 100 ml. of 10% hydrochloric acid. After separation, the organic layer was washed with 10% hydrochloric acid, water, 5% aqueous sodium carbonate, and water, then dried over calcium chloride. Removal of the benzene and unchanged thiophene and purification of the residue (liquids by vacuum distillation and solids by methanol crystallization) afforded the desired ketone. The results are summarized in Table I.

2-n-Alkylthiophenes. A mixture of 0.1 mole of *n*-alkyl 2-thienyl ketone, 30 ml. of 85% hydrazine hydrate and 400 ml. of diethylene glycol was heated to 190° and maintained at that temperature until the water and excess hydrazine hydrate had distilled. After cooling the mixture to 80°, 25 g. of potassium hydroxide was added, the temperature then being raised to, and maintained at, 160° for 3 hr. The mixture was then poured into cold water, extracted with benzene, and the combined benzene extracts washed with water until alkali-free. Following drying of the washed benzene extracts with calcium chloride and removal of the solvent, the product was purified by vacuum distillation. The results are summarized in Table II.

TABLE II

2-*n*-ALKYLTHIOPHENES



R	Yield, %	B.P.
C_7H_{15}	66.6	118–119 (2.5)
C_9H_{19}	64.0	146–149 (3.5)
$C_{13}H_{27}$	77.0	129–130 (0.5)[a]
$C_{15}H_{31}$	90.8	158–160 (0.5)

[a] *Anal.* Calcd.: C, 77.07; H, 11.50; S, 11.43. Found: C, 76.98; H, 11.47; S, 11.30.

Ethyl 9-(5-n-alkyl-2-thenoyl) nonanoates. These were prepared from the 2-*n*-alkylthiophenes and 9-carbethoxynonanoyl chloride by a method analogous to that used for the *n*-alkyl 2-thienyl ketones described previously. All products were purified by methanol crystallization. The results are summarized in Table III.

Ethyl 10-hydroxy-10-(5-n-alkyl-2-thienyl) decanoates. Reduction of the above keto esters with sodium borohydride yielded the corresponding hydroxy esters. The following relative amounts were used: 0.0431 mole of keto ester; 0.013 mole of sodium borohydride; 150 ml. of ethanol. The keto ester was dissolved in warm alcohol, then an ethanolic solution of sodium borohydride was added with stirring. After addition was complete, the solution was stirred at 70–75° for 2 hr. Water and hydrochloric acid were then added and the product was extracted with ether, the extracts water washed and dried, and the solvent evaporated. The hydroxy esters were purified by recrystallization of the residue from an ethanol-water system. The results are summarized in Table IV.

(8) T. F. Grey, J. F. McGhie, and W. A. Ross, *J. Chem. Soc.*, 1502 (1960).

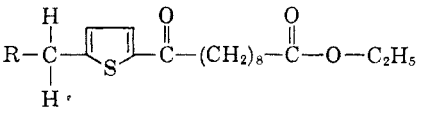
(9) All melting and boiling points recorded in the tables are uncorrected.

(10) J. Cason, *Organic Syntheses*, Coll. Vol. III, 169 (1955).

(11) S. Swann, Jr., R. Oehler, and R. J. Buswell, *Organic Syntheses*, Coll. Vol. II, Wiley, New York, 1943, p. 276.

TABLE III

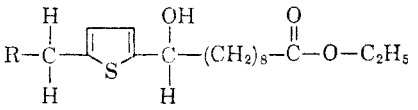
ETHYL 9-(5-*n*-ALKYL-2-THENOYL) NONANOATES



R	Yield, %	M.P.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	S, % Calcd.	S, % Found
C_7H_{15}	77.5	32.5–33.5	70.60	70.50	9.87	9.92	7.85	7.79
C_9H_{19}	65.8	48–49	71.51	71.45	10.15	10.10	7.34	7.36
$C_{13}H_{27}$	61.6	61–62	73.11	73.16	10.63	10.69	6.71	6.73
$C_{15}H_{31}$	36.8	58.5–59.5	73.98	73.93	10.84	10.89	6.17	6.03

TABLE IV

ETHYL 10-HYDROXY-10-(5-*n*-ALKYL-2-THIENYL) DECANOATES[a]

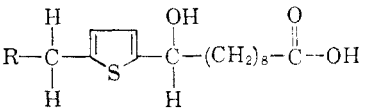


R	Yield, %	M.P.
C_7H_{15}	68.7	—
C_9H_{19}	65.0	—
$C_{13}H_{27}$	88.8	40.5–41.5
$C_{15}H_{31}$	80.8	40–41

[a] All hydroxy esters described were negative toward phenylhydrazine, *p*-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine.

TABLE V

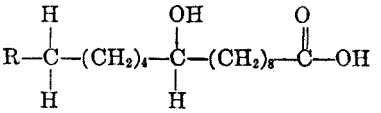
10-HYDROXY-10-(5-*n*-ALKYL-2-THIENYL) DECANOIC ACIDS



R	Yield, %	M.P.	Neut. Equiv. Calcd.	Neut. Equiv. Found
C_7H_{15}	79.0	30–31	384.3	386.1
C_9H_{19}	45.0	57.5–58.5	410.7	412.1
$C_{13}H_{27}$	93.5	61.5–62.5	466.8	466.0
$C_{15}H_{31}$	94.2	76.5–77.5	494.8	494.0

TABLE VI

10-HYDROXY ACIDS



R	Yield, %	M.P.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	OH, % Calcd.	OH, % Found	Neut. Equiv. Calcd.	Neut. Equiv. Found
C_7H_{15}	70.0	83–84	74.10	74.15	12.44	12.38	4.77	4.70	356.6	355.3
C_9H_{19}	71.0	83–84	74.94	74.92	12.58	12.49	4.42	4.31	384.7	383.0
$C_{13}H_{27}$	78.0	92.5–93	76.30	76.26	12.81	12.86	3.86	3.78	440.8	440.0
$C_{15}H_{31}$	88.6	98–99	76.84	76.81	12.90	12.94	3.63	3.60	468.8	467.1

10-Hydroxy-10-(5-n-alkyl-2-thienyl) decanoic acids. The free acids were obtained from the above ethyl esters by saponification with alcoholic potassium hydroxide, followed by acidification with hydrochloric acid. After extraction of the crude product with ether, the extracts were combined, washed, and dried (magnesium sulfate). The solvent was then evaporated to afford the impure acid. Recrystallization of this impure product from petroleum ether (b.p. 30–60°) yielded the purified acid. The results are summarized in Table V.

10-Hydroxy acids. The weights of all thio acids used were based on the introduction of 125 g. of Raney nickel-aluminum alloy powder, the alloy being used in excess.

To a suspension of Raney nickel catalyst (dissolved and digested according to the general method of Bilicka and Adkins[12]) in 150 ml. of ethanol was added the calculated amount of the above described thio acids. The resultant mixture was stirred and refluxed for 14 hr. The catalyst was filtered off and ethanol extracted in a Soxhlet apparatus for 24 hr. The extracts were combined with the original filtrate and the solvent evaporated. The residue was dissolved in aqueous sodium hydroxide and the hydroxy acid precipitated with hydrochloric acid. The organic acid was filtered and washed with water. Recrystallization of this crude acid from dilute ethanol afforded the desired acid. The results are summarized in Table VI.

The hydroxyl analysis mentioned in Table VI was carried out according to the general procedure described by Smith and Shriner.[13]

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(12) H. R. Bilicka and H. Adkins, *Organic Syntheses*, Coll. Vol. III, 176 (1955).

(13) Walter T. Smith, Jr., and Ralph L. Shriner, *The Examination of New Organic Compounds*, Wiley, New York, 1956, p. 112.