dissolved in 50% aqueous acetic acid (400 ml.) and the solution heated on the steam bath. After 1 hr. gas evolution had ceased. The solution was cooled and the precipitate of crude *bis(6-chloro-2-pyridyl)urea* (XVII; 4.5 g., 7.6%, m.p. 230–240°) was removed by filtration. Recrystallization of a sample of XVII from benzene-ethanol gave voluminous white needles, m.p. 250–251°.

Anal. Calcd. for $C_{11}H_8N_4Cl_2O$: C, 46.62; H, 2.83; N, 19.80; Cl, 25.10. Found: C, 46.72; H, 2.81; N, 19.90; Cl, 25.09.

The acetic acid filtrate from the crude urea was cooled (ice bath) and neutralized to *p*H 7 by the gradual addition of 20% aqueous sodium hydroxide. The precipitate (21.2 g.) was filtered, air dried, and sublimed at 75–90° (2 mm.) to give colorless granular crystals of 6-chloro-2-aminopyridine (XV; 18.0 g., 64%; m.p. 65–67°). The melting point was not altered by resublimation.

Anal. Calcd. for $C_5H_5N_2Cl$: C, 46.67; H, 3.91; N, 21.80; Cl, 27.62. Found: C, 47.16; H, 3.99; N, 21.67; Cl, 27.72.

6-Chloro-2-pyridone (XVI). To a stirred and cooled (0–5°) solution of 6-chloro-2-aminopyridine (10.0 g.) in 6*N* sulfuric acid (70.0 ml.) was added, in small portions, solid sodium nitrite (10.0 g.). After careful neutralization of the resulting cold suspension to *p*H 5 with aqueous sodium hydroxide the crude pyridone (9.0 g.) was filtered, washed with a very small amount of ice water and air dried. Recrystallization from benzene (charcoal treatment) afforded the pure pyridone XVI (6.9 g., 70%) as fine white needles, m.p. 125–126° (reported[6] 128.5–129°).

Anal. Calcd. for C_5H_4NOCl: C, 46.40; H, 3.09; N, 10.80; Cl, 27.42. Found: C, 46.43; H, 3.17; N, 10.95; Cl, 27.39.

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COLUMBUS 10, OHIO

[CONTRIBUTION NO. 1368 FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Preparation of Some α-(2-Thienyl)-β-arylethylamines[1]

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A series of seven α-(2-thienyl)-β-arylethylamine hydrochlorides has been prepared from the corresponding ketones by Leuckart reaction. The necessary ketones were made from the arylacetyl chlorides by a Friedel-Crafts reaction with thiophene or from the arylacetonitriles by reaction with 2-thienylmagnesium iodide or 2-thienyllithium.

Reports of the analgesic potentialities of α,β-diphenylethylamines[2–6] suggested the substitution of the 2-thienyl group for either or both phenyl groups in these compounds. The substitution of 2-thienyl for phenyl in physiologically active compounds may result in little or no change in properties[7,8] but occasionally activity is markedly enhanced.[9,10]

The route selected for the preparation of the 2-thienyl isosteres of α,β-diphenylethylamines was *via* the arylacetyl chlorides, employing a Friedel-Crafts reaction to produce the ketones, followed by conversion to the amines with a Leuckart reagent. The necessary arylacetic acids were to be prepared from the hydrocarbons by chloromethylation, cyanation, and hydrolysis. In practice, it was found possible to use this route with phenylacetyl chloride and *p*-methoxyphenylacetyl chloride to give the ketones (I and II, Table I). Stannic chloride and iodine were effective catalysts for the reaction with thiophene. The investigation was also extended to include the 1-naphthyl-substituted ketone (III, Table I). With 2-thienylacetyl chloride,[11] on the other hand, no ketone could be obtained with either stannic chloride or iodine. Hydrogen chloride was freely evolved but only tarry products were obtained. An alternative preparation of the ketone by the use of 2-thienylacetonitrile and 2-thienylmagnesium iodide[12] or 2-thienyllithium[13] also failed, only polymeric materials being obtained. This failure was attributed to the involvement of the α hydrogen atoms of the nitrile. Bisalkylation at the α positions permitted successful reaction to give the ketone (IV, Table I). The corresponding phenyl ketone (V, Table I) was also prepared as well as the diethyl analog (VI, Table I).

Application of a Leuckart reaction was uniformly successful to convert the ketones to the primary amines (VII–XI, Table II). The yield of the amine (XII, Table II) from the diethyl ketone (VI, Table

(1) From the doctoral dissertation of Robert A. Brooks; Yale University; present address: Jackson Laboratory, E. I. du Pont de Nemours and Co., Inc., Wilmington 99, Del.

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TABLE I

The ketones, R—C(=O)—2-thienyl

	R	B.P., °C.	M.P., °C.	Source[a]	% Yield
I	$C_6H_5CH_2$—	165 (5 mm.)	51	AC	82
II	p-$CH_3OC_6H_4CH_2$—	165 (2 mm.)	..	AC	47
III	1-$C_{10}H_7CH_2$—	262 (18 mm.)	85	AC	74,[b] 70[c]
IV	2-$C_4H_3SC(CH_3)_2$—	134 (1.5 mm.)	...	N	...
V	$C_6H_5C(CH_3)_2$—	135 (2 mm.)	87.5	N	70,[d] 44[e]
VI	$C_6H_5C(C_2H_5)_2$—	...	86	N	31,[d] 23[e]

[a] AC: *via* the acid chloride; N: *via* the nitrile. [b] Use of stannic chloride. [c] Use of iodine. [d] Use of 2-thienylmagnesium iodide. [e] Use of 2-thienyllithium.

TABLE II

The Amine Hydrochlorides, R—CH(NHR′·HCl)—2-thienyl

	R	R′	M.P., °C.	Yield, %	Empirical Formula	Nitrogen Anal. Calcd.	Found
VII	$C_6H_5CH_2$—	H	220	56	$C_{12}H_{14}ClNS$	5.84	5.96
VIII	p-$CH_3OC_6H_4CH_2$—	H	...	57	$C_{13}H_{16}ClNOS$	5.19	5.39
IX	1-$C_{10}H_7CH_2$—	H	221	58	$C_{16}H_{16}ClNS$	4.83	5.23
X	2-$C_4H_3SC(CH_3)_2$—	H	243	24[a]	$C_{12}H_{16}ClNS_2$	5.11	5.29
XI	$C_6H_5C(CH_3)_2$—	H	255	42	$C_{14}H_{18}ClNS$	5.23	5.16
XII	$C_6H_5C(C_2H_5)_2$—	H	...	...	$C_{16}H_{21}NS$[b]	5.40	5.17
XIII	$C_6H_5CH_2$—	—CH_3	166	4,[c] 32[d]	$C_{13}H_{16}ClNS$	5.52	5.57

[a] Yield from nitrile. [b] Free amine, hydrochloride unstable. [c] Use of modified Leuckart reaction. [d] Use of Decker reaction.

I) was low. One secondary amine (XIII, Table II) was prepared by a modified Leuckart reaction using *N*-methylformamide and, in better yield, by a Decker reaction.

EXPERIMENTAL

Benzyl 2-thienyl ketone (I) was prepared from phenylacetyl chloride and thiophene using stannic chloride as described by Spurlock.[14] After crystallization from 50% alcohol the ketone was obtained as plates. The *2,4-dinitrophenylhydrazone* melted at 180°.

Anal. Calcd. for $C_{18}H_{14}N_4O_4S$: N, 14.65. Found: N, 14.43.

p-Methoxyphenylacetonitrile was prepared from *p*-methoxyphenylacetyl chloride[15] by reaction with potassium cyanide in boiling acetone containing 10% water; b.p. 93–96° (4 mm.); n_D^{20} 1.5325; yield 75%.

p-Methoxyphenylacetic acid. Hydrolysis of *p*-methoxyphenylacetonitrile gave very low yields of the acid. Consequently, the acid was prepared *via* the imino ester hydrochloride and ester without isolation of these compounds. A solution of 20 g. (0.136 mole) of *p*-methoxyphenylacetonitrile in 6.3 g. (0.136 mole) of absolute alcohol and 50 ml. of ether was treated with 7.5 g. (0.205 mole) of dry hydrogen chloride at 0°. The solution was then allowed to stand in the cold for several hours. Water (50 ml.) was added and the ether was removed. Potassium hydroxide (20 g., 0.357 mole) in 100 ml. of 95% alcohol was added and the solution was refluxed for 3 hr. As much alcohol as possible was removed by distillation at atmospheric pressure on a steam bath. All ether-soluble material was extracted and the remaining solution was made strongly acidic with dilute hydrochloric acid. An oil which separated was dissolved in ether. After drying and removal of the ether the product was obtained as a solid which was crystallized from carbon tetrachloride and petroleum ether; m.p. 86°; yield 14 g. (62%).

p-Methoxyphenylacetyl chloride was prepared from the acid by reaction with thionyl chloride; b.p. 126–130° (14 mm.); yield 90%.

p-Methoxybenzyl 2-thienyl ketone (II). Iodine (0.15 g.) was added to a solution of 8.5 g. (0.046 mole) of *p*-methoxyphenylacetyl chloride in 7.7 g. (0.092 mole) of thiophene. The mixture was shaken until the iodine had dissolved and then was refluxed for 6 hr. A volume of water and two volumes of ether were added. The ether layer was separated, washed with 25 ml. of 5% sodium carbonate solution and with water. After drying, the ether and excess thiophene were removed. Distillation of the residue gave 5 g. of product. Crystallization from 85% alcohol gave needles with no clear cut melting point.

Anal. Calcd. for $C_{13}H_{12}O_2S$: S, 13.80. Found: S, 13.86.

1-(2-Thienyl)-2-(1-naphthyl)ethanone-1 (III). (*a*) A solution of 19 g. (0.073 mole) of stannic chloride in 25 ml. of benzene was cooled to −10° and a solution of 15 g. (0.073 mole) of 1-naphthylacetyl chloride,[16] 6.1 g. (0.073 mole) of thiophene, and 30 ml. of benzene was added during 1.5 hr. The mixture was then stirred at room temperature for 1 hr. Water (50 ml.) containing 1 ml. of concentrated hydrochloric acid was added. The benzene layer was separated, washed with 50 ml. of 5% sodium carbonate solution and with water. After drying, the benzene was removed and the residue distilled. The product was a liquid which solidified on cooling; yield 13.7 g. Crystallization from 80% alcohol raised the melting point to 85°.

(*b*) The use of iodine in place of stannic chloride gave 12.1 g. of product.

Ethyl 2-thienyliminoacetate hydrochloride. Dry hydrogen chloride (1.25 moles) was passed into a solution of 24.6 g.

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(16) F. E. King and T. Henshall, *J. Chem. Soc.*, 417 (1945).

(0.20 mole) of 2-thienylacetonitrile[17] and 9.2 g. (0.20 mole) of absolute alcohol in 50 ml. of ether. During addition of the gas the temperature was maintained at 0°, and following attainment of the correct weight the flask was placed in an ice box. After several hours, clumps of needles formed; m.p. 97.5°; yield 18 g. (43%).

Anal. Calcd. for $C_8H_{12}ClNOS$: N, 6.80. Found: N, 7.07.

Ethyl 2-thienylacetate[18] was prepared by the hydrolysis of ethyl 2-thienyliminoacetate hydrochloride.

2-Thienylacetic acid.[18] Saponification of 11 g. (0.065 mole) of ethyl 2-thienylacetate gave 7.5 g. (81%) of the acid; m.p. 73°. Recrystallization from carbon tetrachloride and petroleum ether yielded plates melting at 76°. Preparation of 2-thienylacetic acid from 2-thienylacetonitrile without isolation of the intermediate imino ester hydrochloride and ester gave an improvement in yield to 88% overall.

2-Thienylacetyl chloride was prepared from 2-thienylacetic acid and thionyl chloride by the method of Cagniant.[11] All attempts to condense this product with thiophene failed to give the ketone.

α-Methyl-(2-thienyl)acetonitrile. (*a*) A solution of 41.3 g. (0.341 mole) of 2-thienylacetonitrile in 250 ml. of ether was cooled to 0°. During 30 min. 13.3 g. (0.341 mole) of powdered sodium amide was added. The mixture was stirred for 15 min. at room temperature and then 48.8 g. (0.341 mole) of methyl iodide was added dropwise. The mixture was refluxed for 2 hr. and hydrolyzed with 200 ml. of cold water. The ether layer was separated and dried. After removal of the ether the residue was distilled to give 25 g. (53%) of liquid; b.p. 94° (10 mm).

(*b*) Substitution of lithium amide for sodium amide in the above procedure gave a 58.5% yield of the nitrile.

Anal. Calcd. for C_7H_7NS: N, 10.21. Found: N, 10.07.

α,α-Dimethyl-(2-thienyl)acetonitrile. (*a*) Sodium amide (7.1 g., 0.182 mole) was suspended in 250 ml. of ether at 0° and, during 1 hr., 25 g. (0.182 mole) of α-methyl-(2-thienyl)acetonitrile was added. The mixture was stirred for 30 min. at room temperature and 25.8 g. (0.182 mole) of methyl iodide was dropped in. The mixture was refluxed for 1 hr., hydrolyzed with 200 ml. of water, and the ether layer separated. After drying the nitrile was distilled; b.p. 93–95° (11 mm); yield 13 g. (47%).

(*b*) Substitution of lithium amide for sodium amide raised the yield to 70.5%.

Anal. Calcd. for C_8H_9NS: N, 9.27. Found: N, 9.16.

1,2-Di-(2-thienyl)-2,2-dimethylethanone-1 (IV). A solution of 40 g. (0.265 mole) of α,α-dimethyl-(2-thienyl)acetonitrile in 100 ml. of ether was added slowly to a solution of 2-thienyllithium prepared from 6.9 g. (1.0 mole) of lithium, 68.5 g. (0.50 mole) of *n*-butyl bromide, and 42 g. (0.50 mole) of thiophene in 150 ml. of ether.[13] The mixture was refluxed for 12 hr. and then poured over ice. The ether layer was separated and dried. After removal of the ether the residue was stirred at 100° with 20% hydrochloric acid for 4 hr. The acidic solution was extracted with ether and the extracts were washed and dried. After removal of the solvent the residue was distilled to give 4 g. of the ketone and 16 g. of unchanged α,α-dimethyl(2-thienyl)-acetonitrile.

Anal. Calcd. for $C_{12}H_{12}OS_2$: S, 27.14. Found: S, 27.35.

It was found possible to substitute 2-thienylmagnesium iodide for 2-thienyllithium in this preparation. Yields were improved by replacing the ether with xylene and heating the reaction mixture at 100° for 18 hr. before hydrolysis. The crude product was used directly in the preparation of the amine (IX).

1-(2-Thienyl)-2-phenyl-2,2-dimethylethanone-1 (V). (*a*) To 0.30 mole of 2-thienyllithium in 500 ml. of ether[13] was added 14.5 g. (0.10 mole) of α,α-dimethylphenylacetonitrile.[19] After refluxing for 12 hr. the reaction mixture was poured over 200 g. of ice mixed with 100 ml. of saturated ammonium chloride solution. The ether layer was separated, washed, and dried. Hydrogen bromide was passed into the ether solution. Five grams of a yellow solid, believed to be the imide hydrobromide of the ketone (V), precipitated. This material was heated for 1 hr. with 25 ml. of 20% hydrochloric acid. The precipitated oil was dissolved in ether. After removal of the ether the gummy residue was crystallized from 95% alcohol. Needles were obtained; yield 3.2 g. The ether solution from which the hydrobromide had precipitated was distilled to remove the solvent and the residue was heated at 100° for 1 hr. with 100 ml. of 20% hydrochloric acid. The mixture was extracted with ether and the extracts were dried. After removal of the ether the product was distilled and crystallized from 95% alcohol; yield 7 g. The phenylhydrazone was prepared and crystallized from 90% alcohol.

Anal. Calcd. for $C_{20}H_{20}N_2S$: N, 8.74. Found: N, 8.70.

(*b*) To 0.20 mole of 2-thienylmagnesium iodide in 250 ml. of ether[12] was added 6 g. (0.041 mole) of α,α-dimethylphenylacetonitrile. The solution was refluxed briefly and then the ether was replaced by xylene. The xylene solution was heated at 100° for 12 hr., refluxed for 2 hr. and distilled to remove the xylene. The residue was hydrolyzed with ice and then heated at 100° for 1 hr. with 150 ml. of 20% hydrochloric acid. The product was dissolved in ether and dried. After removal of the ether the product was distilled; yield 6.6 g.

1-(2-Thienyl)-2-phenyl-2,2-diethylethanone-1 (VI). (*a*) To 0.30 mole of 2-thienyllithium in 500 ml. of ether was added 17.3 g. (0.10 mole) of α,α-diethylphenylacetonitrile.[20] After refluxing for 16 hr. the reaction mixture was hydrolyzed with ice and dilute hydrochloric acid. The ether layer was dried and the ether removed. The residual oil was stirred at 100° for 1 hr. with 100 ml. of 25% hydrochloric acid. Eight grams of a solid precipitated on cooling and was filtered. This was the hydrochloride of the ketimine of the ketone (VI). It was soluble in hot 95% alcohol, gave a precipitate with silver nitrate and reacted with potassium hydroxide to give a brown oil. Prolonged boiling with dilute alcohol followed by cooling caused the precipitation of the ketone; yield 6 g.

(*b*) The use of 2-thienylmagnesium iodide in place of 2-thienyllithium as described for the ketone (V) increased the yield to 8 g.

Anal. Calcd. for $C_{16}H_{18}OS$: S, 12.40. Found: S, 12.54.

Preparation of the amines. The following procedure is typical of those used to prepare the primary amines found in Table II. *α-(2-Thienyl)-β-phenylethylamine hydrochloride* (VII). Twenty-four grams of 85–90% formic acid was added dropwise to 24 g. of powdered ammonium carbonate. The mixture was slowly distilled until the temperature reached 165°. Then 20.2 g. (0.10 mole) of benzyl 2-thienyl ketone (I) was added. The temperature was raised to 180–185° and maintained for 8 hr. Two volumes of water were added to the cooled mixture which caused solidification. The water was decanted, 20 ml. of concentrated hydrochloric acid was added, and the mixture was refluxed for 1 hr. Two hundred ml. of water and 200 ml. of ether were added, the water layer was separated and treated with 2 g. of activated charcoal. Filtration gave a light brown solution which was made basic with sodium hydroxide. The precipitated oil was dissolved in ether. After washing and drying, the ether solution was saturated with hydrogen chloride. A precipitate of 13.4 g. was dissolved in absolute alcohol and reprecipitated with ether. A sample was treated with alkali to liberate the base; b.p. 171° (10 mm). Another sample was converted to the acetyl derivative; m.p. 99–100°.

Anal. Calcd. for $C_{14}H_{15}NOS$: N, 5.71. Found: N, 5.67.

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N-Methyl-α-(2-thienyl)-β-phenylethylamine hydrochloride (XIII). (*a*) A mixture of 20.2 g. (0.10 mole) of benzyl 2-thienyl ketone (I) and 23.6 g. (0.40 mole) of *N*-methylformamide was refluxed for 12 hr. Two volumes of water were added, the organic layer was separated and refluxed for 2 hr. with 30 ml. of concentrated hydrochloric acid. Water (50 ml.) was added and the mixture extracted with two 75-ml. portions of ether. After drying, the extracts were saturated with hydrogen chloride. An oil which separated was dissolved in absolute alcohol and ether was added to precipitate the product; yield 1.1 g.

(*b*) α-(2-Thienyl)-β-phenylethylamine (22 g., 0.108 mole) and 11.5 g. (0.108 mole) of benzaldehyde were warmed for 15 min. on a steam bath. Water which was liberated was removed under vacuum. Then 15.3 g. (0.108 mole) of methyl iodide was added. The resulting solution was heated at 100° for 12 hr. in a sealed tube. The reaction mass was boiled for 30 min. with 50 ml. of 95% alcohol, the alcohol was removed, and 100 ml. of water was added. This solution was filtered, treated with 2 g. of activated charcoal, filtered, and cooled. The addition of sodium hydroxide caused an oil to separate which was extracted with 100 ml. of ether. The extract was dried and mixed with 50 ml. of anhydrous ether saturated with hydrogen chloride. A precipitate which formed was dissolved in a minimum of absolute alcohol and reprecipitated with ether; yield 9 g.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DOW CHEMICAL CO., EASTERN RESEARCH LABORATORY]

Aminophenols. I. The Reaction of *o*-Aminophenol with Chloracetic Acid and Some Comments on the Formation of Phenmorpholones[1]

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The reaction between *o*-aminophenol and chloroacetic acid has been reinvestigated; the products obtained have been identified, their structures proved, and optimum conditions of formation established. A number of examples are presented of the ring-closure of *o*-hydroxyphenylglycines and *o*-aminophenoxyacetic acids to 2- and 3-phenmorpholones, respectively, and the similarity to the ring-chain tautomerism of α-(β-hydroxyethylamino)ketones is noted.

Vater[2] reported that *N*-(*o*-hydroxyphenyl)glycine (I) may be prepared by the alkylation of *o*-aminophenol with chloroacetic acid. Repetition of his work yielded an entirely different product and, inasmuch as no published account more recent than Vater's[2] is available, we investigated the reaction in some detail. We now find that by varying the experimental conditions there may be isolated at least five major products (I–V), all in yields of 60% or better.

Though the reaction of mono- or disubstituted amines with chloroacetic acid in the presence of a suitable acid acceptor is a well known method for the preparation of *N*-mono- and disubstituted glycines,[3] it is usually difficult to stop the reaction at the introduction of a single acetic acid group, and separation of the mono- from the diproduct can be tedious.[4] In general, the formation of the monoglycine is favored by an excess of amine,[5] while the diglycine is usually obtained in good yield when excess chloroacetic acid is used.[6] When no added base is present (hydroxide, acetate, etc.) then the amine itself acts as acceptor of the acid liberated and, to avoid decreasing the yield, must be present in excess. These principles are demonstrated amply in the discussion which follows.

The introduction of a mono- or dicarboxymethyl group in *o*-aminophenol (as in I or IIa) offers a favorable opportunity for intramolecular lactonization of the carboxyl with the *o*-phenolic function to form the stable six membered phenmorpholone ring. However, the fact that we found this condensation to be remarkably facile in specific cases only, prompted us to extend our investigations to related systems and to correlate these with some previously reported ring closures. Thus, the formation of 2- and 3-phenmorpholones from *o*-hydroxyphenylglycines and *o*-aminophenoxyacetic acids is presented as a logical adjunct to our study of the reaction of *o*-aminophenol with chloroacetic acid.

Formation of the products. Table I represents a summary of the products obtained from over 20 runs in which the experimental conditions and ratio of reagents were varied systematically. The products, or mixtures, obtained from this reaction are controlled largely by two factors: (1) the ratio of the reactants, *o*-aminophenol and chloroacetic acid, and (2) the *p*H of the solution. That both these factors are equally important can be seen from a casual inspection of Table I. Thus, for example, maintaining the ratio of reactants constant and changing the *p*H slightly, as in runs 3 and 4, give different products, and this is equally true of runs 6 and 8 where the *p*H is constant and the ratio is changed.

Since chloroacetic acid is a strong acid, the *p*H

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(1) Presented in part before the Organic Section of the 131st Meeting of the American Chemical Society, Miami, Fla. April 1957.

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