TABLE I

	Formula	Chlorine, % Calcd.	Found	M.p., °C.
1-Methylpyridinium chloroferrate(III)	$C_6H_8NFeCl_4$	48.6	48.3	148–148.5[2]
1-Benzylpyridinium chloroferrate(III)	$C_{12}H_{12}NFeCl_4$	38.6	38.2	80
1,2-Dimethylpyridinium chloroferrate(III)	$C_7H_{10}NFeCl_4$	46.4	46.5	193–194
1,4-Dimethylpyridinium chloroferrate(III)	$C_7H_{10}NFeCl_4$	46.4	46.3	118–118.5
1-Methyl-2-benzylpyridinium chloroferrate(III)	$C_{13}H_{14}NFeCl_4$	37.2	36.9	70
1,2,6-Trimethylpyridinium chloroferrate(III)	$C_8H_{12}NFeCl_4$	44.4	44.1	204–205[3]
1-Methylquinolinium chloroferrate(III)	$C_{10}H_{10}NFeCl_4$	41.5	41.2	195–196
1,2-Dimethylquinolinium chloroferrate(III)	$C_{11}H_{12}NFeCl_4$	39.9	39.6	165–166
1-Methyl-6-methoxyquinolinium chloroferrate(III)	$C_{11}H_{12}NOFeCl_4$	38.2	37.9	97–98
2-Methyl-3,5-diphenylisoxazolium chloroferrate(III)	$C_{16}H_{14}NOFeCl_4$	32.7	32.4	108.5–109
2-Methyl-3-phenyl-5-*p*-bromophenylisoxazolium chloroferrate(III)				143–144[4]
2-Methyl-3-*p*-bromophenyl-5-phenylisoxazolium chloroferrate(III)				139–140[4]
2-Methyl-3,4,5-triphenylisoxazolium chloroferrate(III)				162[5]

2-Methyl-3-*p*-bromophenyl-5-phenylisoxazolinium chloroferrate(III), m.p. 115–116°, calcd. for $C_{16}H_{15}BrNOFeCl_4$: C, 37.3; H, 2.94. Found: C, 37.4; H, 2.66.

2,5-Dimethyl-3-phenylbenzisoxazolium chloroferrate(III), m.p. 95–96°, calcd. for $C_{15}H_{14}NOFeCl_4$: C, 42.70; H, 3.3 Found: C, 42.85; H, 3.1.

3,5-Dimethyl-2-phenylbenzoxazolium chloroferrate(III), m.p. 142–143°, calcd. for $C_{15}H_{14}NOFeCl_4$: C, 42.7; H, 3.3. Found: C, 42.6; H, 3.2.

to hydrolyze the excess ester, and concentrated aqueous ferric chloride solution is added until precipitation of the salt is complete. The intermediate methosulfate and chloride are not isolated. This procedure works not only for those heterocyclic compounds like pyridine and picoline that react vigorously with dimethyl sulfate, but also for such highly hindered and weakly basic heterocycles as 3,4,5-triphenylisoxazole. If the heterocyclic compound reacts too vigorously with dimethyl sulfate, benzyl chloride can be used instead: 1-benzylpyridinium chloroferrate(III) is an example of a derivative prepared by this variant procedure.

The chloroferrates(III) that we have prepared (Table I) are yellow solids, varying from greenish-yellow to orange-yellow. They are sparingly soluble in glacial acetic acid at room temperature and quite soluble by comparison in the same solvent hot, so that they are readily purified by crystallization from acetic acid. Most of them are conveniently analyzed for ionic chlorine by the Volhard procedure and, since they contain ferric iron, it is not necessary to add an indicator. The chloroferrates(III) from the heterocyclic compounds that contain oxygen as well as nitrogen in the ring develop purple colored solutions on addition of silver nitrate. With these colored solutions the end-point on titration with thiocyanate is not readily determined. Carbon and hydrogen analyses are therefore preferred, although the alternative procedure of ashing and determining iron can be used.

The salts listed in Table I were prepared either because we needed them for identification or because the heterocyclic compounds were available to us. They do not constitute an exhaustive test of the usefulness of the chloroferrates(III). Although such a test will have to wait upon more extended use of these derivatives, we can indicate the limitations we have observed so far. One heterocyclic compound, 3,5-diphenylisoxazoline, yielded an oil rather than a crystalline chloroferrate(III). The chloroferrates(III) from two compounds that contained more than one C=N linkage [2,3-diphenylquinoxaline and 1,4-bis-(6,7-dimethoxy-1-isoquinolyl)-butane] did not have good physical properties. Otherwise we have encountered no complications in the preparation and use of the chloroferrates(III).

(2) M. Scholtz, *Arch. Pharm.*, **247**, 5 (1904), prepared this chloroferrate(III) but did not report a melting point.

(3) R. Lukeš and M. Jureček, *Chem. Listy*, **37**, 177 (1943); *C. A.* **39**, 2505 (1945).

(4) A. H. Blatt, THIS JOURNAL, **71**, 1862 (1949).

(5) E. P. Kohler and A. H. Blatt, *ibid.*, **50**, 1222 (1928).

Experimental

It is convenient to add liquid heterocyclic compounds (*e.g.*, pyridine) dropwise to excess dimethyl sulfate and to add dimethyl sulfate to solid heterocyclic compounds. The usual quantities are 0.5 ml. or g. of the heterocyclic compound and 1.5 ml. of dimethyl sulfate. These reactants are heated on a steam-bath for three hours then left to cool. Five ml. of hydrochloric acid (one part concentrated acid and one part water) is added and, after the excess dimethyl sulfate has been hydrolyzed, 5 ml. of ferric chloride solution (two parts of $FeCl_3 \cdot 6H_2O$ in one part of water) is added.

Usually the salt crystallizes at once. Occasionally it appears as an oil that crystallizes on standing overnight. The crystalline salt is filtered, washed with a little glacial acetic acid, and crystallized from the same solvent.

Reactive heterocyclic compounds add dimethyl sulfate in less than the three hours prescribed above. If the heterocyclic compound is heavily substituted near the C=N linkage, longer heating may be necessary. A convenient test for completeness of reaction is the formation of a clear solution when the excess dimethyl sulfate has been hydrolyzed.

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3-Substituted Thiophenes. X. Barbituric Acid Derivatives[1]

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The 2-thienyl analog of phenobarbital, 5-(2-thienyl)-5-ethylbarbituric acid, was prepared by Blicke and Zienty,[2] and found to have the same order of activity as phenobarbital in the rat, being slightly less hypnotic but also slightly less toxic. 5-(2-Thenyl)-5-ethylbarbituric acid, prepared by Owen and Nord,[3] was found to be qualitatively

(1) Contribution No. 679. Taken from part of a thesis submitted by R. L. Patrick in partial fulfillment of the requirements for the degree Doctor of Philosophy at Indiana University, June, 1950.

(2) F. F. Blicke and M. F. Zienty, THIS JOURNAL, **63**, 2945 (1941).

(3) L. J. Owen and F. F. Nord, *J. Org. Chem.*, **15**, 988 (1950).

similar to its benzyl analog in causing convulsions,[4] but the thiophene derivative was again apparently less active and less toxic than the corresponding benzene compound. It was therefore interesting to prepare some 3-thienyl substituted barbituric acids, in order to compare their physiological activities with that of the 2-thienyl and phenyl analogs.

The synthesis of the desired barbituric and 2-thiobarbituric acids was accomplished in satisfactory yields by the conventional condensation of substituted malonic esters and urea or thiourea in the presence of ethoxide ions. The intermediate substituted malonic esters were prepared by alkylating diethyl 3-thenylmalonate[5] or diethyl 3-thienylmalonate in the usual manner. Diethyl 3-thienylmalonate was prepared by carbethoxylation of ethyl 3-thienylacetate, using diethyl oxalate to form the oxaloacetate which then was decarbonylated.

Although the substituted barbituric acids are frequently recrystallized from water, apparently the formation of hydrates is not commonly encountered. However, in the course of this investigation, two compounds were isolated from water solutions which analyzed correctly for hydrates. These compounds retained water very tenaciously, and may actually have different structures. When diethyl ethyl-(3-thenyl)-malonate was condensed with urea, two products were isolated by fractional crystallization from water. The lower melting compound analyzed correctly for the desired barbituric acid, and produced the expected result in experimental animals. The higher melting product analyzed quite well for a monohydrate of 5-ethyl-5-(3-thenyl)-barbituric acid. However, efforts to dehydrate this compound were unsuccessful, as were efforts to form the hydrate by repeatedly recrystallizing the lower melting compound from water. Unfortunately the pharmacological tests were not carried out on this compound. When diethyl 3-thenalmalonate was condensed with urea, bright yellow crystals were obtained which melted at 161–162°. Analysis indicated that this product, which behaved in other respects like a barbituric acid, contained two molecules of water. Previous investigators[3,6,7] have commented on the unusual properties of the benzalbarbituric acids. These compounds are brightly colored, insoluble in organic solvents, and have abnormal melting points. For example, the 2-thenal derivative melts with decomposition at 330–333°,[3] and the 2-furanal derivative decomposes above 280°.[6] No mention was made of hydrate formation, however. In view of the low melting point and analysis of our product, it seems unlikely that this substance is a true thenalbarbituric acid.

The barbituric acids were tested for hypnotic activity through the courtesy of the Sterling–Winthrop Research Institute. Like their 2-thenyl analogs, the 5-(3-thenyl)-5-alkylbarbituric acids produced convulsions in rats in doses of 100 mg./kg. However, 5-ethyl-5-(3-thienyl)-barbituric acid was qualitatively different from its 2-thienyl isomer[2] in that it produced sedation but no hypnosis or analgesia at dose levels of 100, 140 and 200 mg./kg.

(4) H. A. Shonle and A. Moment, THIS JOURNAL, **45**, 243 (1923).

(5) E. Campaigne and W. C. McCarthy, *ibid.*, **76**, 4466 (1954).

(6) M. Conrad and H. Reinbach, *Ber.*, **34**, 1339 (1901).

(7) A. W. Dox and G. P. Plaisance, THIS JOURNAL, **38**, 2164 (1916).

Experimental

Ethyl 3-Thienylacetate.—A mixture of 56 ml. of concd. sulfuric acid dissolved in 186 ml. of absolute ethanol and 112 g. (0.91 mole) of 3-thienylacetonitrile[5] was refluxed for seven hours, cooled, and poured into 200 ml. of water. After washing and drying the oily layer which separated, it was distilled through a short Vigreux column, and 89.5 g. (62%) of a colorless oil boiling from 107–115° at 6 mm. was obtained.

Anal. Calcd. for $C_8H_{10}O_2S$: S, 20.06. Found: S, 19.91.

Diethyl 3-Thienylmalonate.—A procedure was used similar to that described by Vogel[8] for the phenyl analog. When 79 g. (0.49 mole) of ethyl 3-thienylacetate was treated with 73 g. (0.5 mole) of freshly distilled diethyl oxalate in the manner described, a nearly quantitative yield of crude diethyl 3-thienyloxaloacetate was obtained. This crude product was not purified, but was decarbonylated directly. Slow decarbonylation at 210° for six hours, as described by Vogel,[8] yielded 55 g. (45%) of redistilled diethyl 3-thienylmalonate. The use of powdered soft glass in the decarbonylation reaction caused a much more rapid evolution of carbon monoxide, but the yield of product was only 29%.

Alkylation of Thenyl- and Thienylmalonates.—Diethyl 3-thenylmalonate, prepared as previously described,[5] was obtained in much better yield (81%) when freshly distilled 3-thenyl bromide[9] was used in its preparation. This compound was converted to its sodium salt in absolute ethanol, and alkylated with ethyl iodide or allyl bromide, as described by Vogel.[8] In the same way, the ethyl- and allyl-3-thienylmalonic esters were prepared by alkylation of diethyl 3-thienylmalonate. The pertinent data on the preparation of the malonic esters are presented in Table I.

TABLE I

MALONIC ESTERS CONTAINING THE 3-THIENYL SUBSTITUENT $RR^1C(COOC_2H_5)_2$

R	R^1	B.p. °C.	Mm.	Yield, %	Formula	Sulfur, % Calcd.	Found
3-Thenyl	H	141–147	4	81[5]	$C_{12}H_{16}O_4S$	12.46	12.32
3-Thenyl	Ethyl	160–164	5	54	$C_{14}H_{20}O_4S$	11.29	11.14
3-Thenyl	Allyl	155–157	3	73	$C_{15}H_{20}O_4S$	10.81	10.80
3-Thienyl	H	151–152	2	45	$C_{11}H_{14}O_4S$	13.24	13.68
3-Thienyl	Ethyl	172–174	4	45	$C_{13}H_{18}O_4S$	11.84	11.80
3-Thienyl	Allyl	158–159	6	50	$C_{14}H_{18}O_4S$	11.34	11.29

Diethyl 3-Thenalmalonate.—Using the method of Allen and Spangler[10] for the benzal analog, a mixture of 71.4 g. (0.44 mole) of freshly distilled diethyl malonate, 37 g. (0.46 mole) of freshly distilled 3-thenaldehyde,[11] 4 ml. of piperidine and 1.5 g. of 3-thenoic acid dissolved in 100 ml. of dry benzene was refluxed for 24 hours, during which time only 4 ml. of water was collected in the moisture trap. After washing and drying the benzene solution it was distilled, and 57 g. (51%) of diethyl 3-thenalmalonate, boiling from 179–180° at 7 mm., $n^{25}D$ 1.5491, was collected.

Anal. Calcd. for $C_{12}H_{14}O_4S$: S, 12.61. Found: S, 11.98.

Barbituric Acids.—All of the substituted malonic esters in Table I were converted to the corresponding barbituric acids by the sodium ethoxide catalyzed condensation with urea, followed by recrystallization from water, as described by Vogel.[12] Substitution of thiourea for urea in this preparation gave adequate yields of the desired 2-thiobarbituric acids.

The isolation of 5-ethyl-5-(3-thenyl)-barbituric acid presented a difficulty not encountered in the other preparations. When 17.4 g. (0.06 mole) of ethyl-(3-thenyl)-malonic ester was treated with excess urea in the usual manner, and the barbituric acid precipitated in aqueous acid, 15 g. of crude product, which melted from 150–164°, was obtained. This

(8) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 869.

(9) E. Campaigne and B. F. Tullar, *Org. Syntheses*, **33**, 96 (1953).

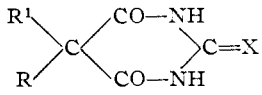
(10) C. F. H. Allen and F. W. Spangler, *ibid.*, **25**, 42 (1945).

(11) E. Campaigne, R. C. Bourgeois and W. C. McCarthy, *ibid.*, **33**, 93 (1953).

(12) Reference 8, page 870.

TABLE II

BARBITURIC ACIDS CONTAINING THE 3-THIENYL SUBSTITUENT



R	R¹	X	M.p., °C.	Yield, %	Formula	Sulfur, % Calcd.	Sulfur, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3-Thenyl	H	O	207–207.5	95	$C_9H_8O_3N_2S$	14.30	13.96	12.50	12.55
3-Thenyl	Ethyl	O	162–163	20[a]	$C_{11}H_{12}O_3N_2S$	12.71	13.05	11.11	11.05
3-Thenyl	Allyl	O	155.5–156.5	77	$C_{12}H_{12}O_3N_2S$	12.13	11.85	10.60	11.04
3-Thenyl	Ethyl	S	170–171	57	$C_{11}H_{12}O_2N_2S_2$	23.89	23.81	10.44	10.32
3-Thenyl	Allyl	S	155–155.5	55	$C_{12}H_{12}O_2N_2S_2$	22.86	22.71	9.99	9.75
3-Thienyl	Ethyl	O	192–194	45	$C_{10}H_{10}O_3N_2S$	13.45	13.40	11.76	11.92
3-Thienyl	Allyl	O	133–134	31	$C_{11}H_{10}O_3N_2S$	12.82	12.64	11.20	11.01

[a] After separation of hydrate.

crude product was dissolved in 10% sodium carbonate and reprecipitated with hydrochloric acid without much loss in weight or improvement in melting range. Careful fractional crystallization from water gave 3 g. of white glistening plates, melting at 177–178° without decomposition, which analyzed correctly for a monohydrate.

Anal. Calcd. for $C_{11}H_{12}O_3N_2S \cdot H_2O$: S, 11.86; N, 10.37. Found: S, 11.70; N, 10.21.

Several attempts to dehydrate this material by vacuum desiccation or recrystallization from absolute ethanol were unsuccessful. Concentration of the aqueous mother liquors and cooling caused the deposition of 2.9 g. of crystals melting at 162–163° which analyzed correctly for the desired product. Properties of the barbituric acids are reported in Table II.

Attempted Preparation of 5-(3-Thenal)-barbituric Acid.—When 25.4 g. (0.1 mole) of diethyl 3-thenalmalonate was allowed to react with urea in the usual way, 17.4 g. of a bright yellow crystalline product was obtained which melted at 161–162° after recrystallizing from water. Attempted recrystallization from absolute ethanol resulted in extensive decomposition, and vacuum desiccation at 100° did not alter the compound. It was soluble in 10% sodium carbonate solution with the evolution of carbon dioxide, and was reprecipitated with acid. This substance analyzed correctly for a dihydrate of thenalbarbituric acid.

Anal. Calcd. for $C_9H_8O_3N_2S \cdot 2H_2O$: S, 12.42; N, 10.85. Found: S, 12.26; N, 10.81.

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The Preparation of β-Aminoglutaric Acid and β-Aminoadipic Acid

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Prior to 1953, β-aminodicarboxylic acids were not mentioned in the chemical literature. Recently, a number of publications have appeared on the preparation of this class of compounds. The syntheses[2–4] are based on the reduction of substituted hydrazones of the appropriate β-keto esters, on the action of hydrazoic acid upon β-substituted γ-keto esters[5] such as ethyl cyclopentanone-2-acetate and on the oxidative cleavage[6] of 4-acetamidocyclohexanol. Some of these methods are rather tedious; in many cases the yields are low, and the starting materials are not readily available.

None of these workers seem to have considered the addition of ammonia to an activated double bond in an acid or an acid derivative, although Scheibler[7] had prepared β-aminobutyric acid from crotonic acid and ammonia more than 40 years ago.

In preliminary experiments a 7.7% yield of β-aminoglutaric acid (I) resulted when diethyl glutaconate (II) was heated at 100–110° for 20 hours with excess ammonium hydroxide in a sealed tube. Ruheman[8] had investigated this reaction with II and its α-benzyl derivative and reported the isolation of an unspecified amount of "benzyldihydroxypyridine" from the latter reaction.

A 60% yield of diethyl β-aminoglutarate(III) was realized when ammonia was introduced into an anhydrous ethanol solution of II. The presence of excess ammonia at all times apparently suppressed the formation of secondary and tertiary amino esters that could result from further reactions of III with the unsaturated ester; no trace of these potential by-products was found.

The preparation of I also was attempted *via* addition of phthalimide to II. This method had been employed successfully for the preparation of β-amino acids from unsaturated nitriles[9] or aldehydes.[10] However, all efforts to effect the addition were unsuccessful. Reactions were carried out in ethanolic solutions of sodium ethoxide and *t*-butyl alcohol solutions of potassium *t*-butoxide at both 30° and the reflux temperatures of the solvents (78 and 83°, respectively).

There are two reports[11–12] in the literature which describe the addition of amines to 2-hexenedinitrile, the latter being obtained by isomerization of 3-hexenedinitrile (IV). Langkammerer found that ammonia and primary amines did not give the expected products. However, when compound IV was suspended in excess ammonium hydroxide, and gaseous ammonia was passed through the solution, β-aminoadipic acid was isolated in yields of 40.5 and 62%, depending on the methods employed for isolating the free acid.

(1) Abstracted from a thesis by William A. Swarts submitted to the Faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) J. Gootjes and W. Th. Nauta, *Rec. trav. chim.*, **72**, 721 (1953).

(3) L. Birkofer and I. Storch, *Chem. Ber.*, **86**, 32 (1953).

(4) A. Romeo and L. Magni, *Atti acad. nazl. Lincei, Rend., Classe. sci. fis., mat. e nat.*, **14**, 423 (1953); *C. A.*, **48**, 10592 (1954).

(5) L. Birkofer and I. Storch, *Chem. Ber.*, **86**, 749 (1953).

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(7) H. Scheibler, *Ber.*, **45**, 2278 (1912).

(8) S. Ruheman and R. S. Morrell, *J. Chem. Soc.*, **59**, 743 (1891); **63**, 259 (1893).

(9) V. M. Rodionov and N. G. Yartseva, *Bull. acad. sci., U.R.S.S., Classe sci. chim.*, 251 (1948); *C.A.*, **42**, 4942 (1948).

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(11) C. M. Langkammerer, U. S. Patent 2,532,561 (1950); *C. A.*, **45**, 2967 (1951).

(12) H. F. Piepenbrink, *Ann.*, **572**, 83 (1951).