[CONTRIBUTION NO. 678 FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

3-Substituted Thiophenes. IX.[1] 3-Thienones and 5-(3-Thienyl)-hydantoins[2]

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Several 3-thienones, including 3-benzothienone, 3-(2'-theno)-thienone, 3-propanothienone, 3-butanothienone and 3-pentanothienone, and their derivatives have been prepared and characterized. Using these as intermediates, a series of seven 5-substituted-5-(3-thienyl)-hydantoins has been prepared and characterized. A second series of seven 1-substituted 5-(3-thienyl)-hydantoins has been obtained from 3-thenaldehyde and various alkylamines. Preliminary pharmacological tests indicate that the 3-thienylhydantoins have the same order of activity as anticonvulsants as the phenyl analogs, but are generally less toxic. They are more active and less toxic than the 2-thienyl isomers.

In view of the effectiveness of several 5-phenylhydantoins, such as 5-ethyl-5-phenylhydantoin (Nirvanol), 5,5-diphenylhydantoin (Dilantin) and 3-methyl-5-ethyl-5-phenylhydantoin (Mesantoin) as anticonvulsants in clinical practice, there has been considerable interest in substituted hydantoins having a thienyl group in the 5-position. Spurlock[4] patented a series of 5-substituted-5-(2-thienyl)-hydantoins, and one of these, 5-phenyl-5-(2-thienyl)-hydantoin, was eventually used clinically for a time under the name Thiantoin. It was found to have a favorable therapeutic ratio, since, although it was less active, it was also less toxic than its phenyl analog, Dilantin.[5] Spurlock also studied a series of N-alkylated 5-(2-thienyl)-hydantoins,[6] and found that N-alkylation reduced the anticonvulsant activity in every case. Bywater and Coleman[7] have patented 5,5-di-(2-thienyl)-hydantoin, which proved to be less active and less toxic than Thiantoin.[8] Long, Miller and Chen[9] found a fair degree of anticonvulsant activity in a series of 1-alkyl-5-(2-thienyl)-hydantoins, although none were as active as Dilantin.

In a series of studies carried out in these laboratories, and in laboratories of the Sterling–Winthrop Research Institute, we have demonstrated that when a 3-thienyl group is substituted for a 2-thienyl group in a physiologically active compound, the activity of the 3-thienyl isomer is equal to, or greater than, that of the 2-thienyl derivative. In no case has decreased activity been observed in going from the 2- to the 3-thienyl substituent. Examples of equal activity are found in the local anesthetic activity of dialkylaminoalkyl esters of the thenoic acids,[10] and the antispasmodic activity of alkamine esters of the phenylthienylglycolic acids.[11] Substitution of 3-thienyl for 2-thienyl in the antihistaminics of the ethylenediamine series increased the activity by a factor of 3–5.[12] Similarly the anti-phenylalanine activity of the thienylalanines favors the 3-isomer by a factor of two.[13] In this connection, Dittmer[14] also has commented on the higher activity of 3-thienyl analogs over the 2-substituted isomers. 3-Thienylethylamine has about three times the pressor potency of the 2-isomer,[15] while 3-thienylacetic acid is much more active as a plant hormone than either the 2-isomer or the benzene analog.[16]

It became a matter of great interest, then, considering the high order of anticonvulsant activity of the 2-thienylhydantoins and the likely increase in therapeutic ratio which might be observed, to prepare certain 5-(3-thienyl)-hydantoins and test them as anticonvulsants.

In order to accomplish the desired syntheses, it was necessary to have on hand a number of 3-thienyl ketones. Only a few of these, in which the thiophene ring is unsubstituted in the 2- and 5-positions, are known. 3-(3'-theno)-thienone was prepared in low yield by the dry distillation of the calcium salt of 3-thenoic acid.[17] 3-Acetothienone and 3,3'-thenoin also have been reported,[18] as has 3-mandelothienone and benz-3-thenil.[11] More recently, 3-benzothienone was obtained in small yield by the decarboxylation of 3-benzoyl-2-thenoic acid.[19]

A vast number of 2-thienyl ketones have been prepared[20] by means of the Friedel–Crafts reaction between acyl or aroyl halides and thiophene. Unfortunately, this excellent preparative method is of no value in the 3-thienyl series unless the more reactive 2- and 5-positions are blocked. To obtain the simple 3-thienyl ketones, it was necessary to start with a functional group already present in the 3-position. By reversing the reagents, 3-

(1) For a previous paper in this series see E. Campaigne and W. C. McCarthy, THIS JOURNAL, **76**, 4466 (1954).

(2) Taken in part from the thesis submitted by H. Landon Thomas in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University, February, 1952.

(3) Sterling–Winthrop Fellow in Chemistry, 1950–1951.

(4) J. J. Spurlock, U. S. Patent 2,366,221 (Jan. 2, 1945); *C. A.*, **39**, 1736 (1945).

(5) *Cf.* E. A. Swinyard, W. C. Brown and L. S. Goodman, *J. Pharm. Exptl. Therap.*, **106**, 319 (1952).

(6) J. J. Spurlock, THIS JOURNAL, **75**, 1115 (1953).

(7) W. G. Bywater and W. R. Coleman, U. S. Patent 2,468,168 (Apr. 26, 1949); *C. A.*, **43**, 5805 (1949).

(8) Private communication from Dr. L. M. Long, Parke–Davis and Co.

(9) L. M. Long, C. A. Miller and C. Chen, THIS JOURNAL, **71**, 669 (1949).

(10) E. Campaigne and W. M. LeSuer, *ibid.*, **70**, 3498 (1948).

(11) E. Campaigne and R. C. Bourgeois, *ibid.*, **75**, 2702 (1953).

(12) (a) E. Campaigne and W. M. LeSuer, *ibid.*, **71**, 333 (1949); (b) A. M. Lands, J. O. Hoppe, O. H. Siegmund and F. P. Luduena, *J. Pharm. Exptl. Therap.*, **95**, 45 (1949).

(13) R. G. Garst, E. Campaigne and H. G. Day, *J. Biol. Chem.*, **180**, 1013 (1949).

(14) K. Dittmer, THIS JOURNAL, **71**, 1205 (1949).

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

(16) In a private communication, R. W. Leeper, of the Pineapple Research Institute of Hawaii, reports that 2-thienylacetic acid is inactive, phenylacetic acid has 66%, and 3-thienylacetic acid 141% of the activity of 1-naphthaleneacetic acid in the split-pea test.

(17) W. Steinkopf and H. F. Schmitt, *Ann.*, **533**, 264 (1938).

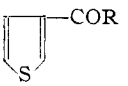
(18) E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948). 3,3'-Thenoin is listed erroneously as 2,3'-thenoin in the book by H. D. Hartough, "Thiophene and Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 325.

(19) B. R. Baker, J. P. Joseph, R. E. Schaub, F. J. McEvoy and J. H. Williams, *J. Org. Chem.*, **18**, 138 (1953).

(20) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, pp. 340–360.

TABLE I

3-THIENYL KETONES



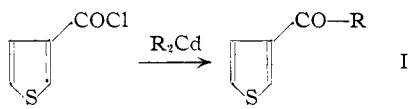
R	B.p., °C.	Mm.	Yield, %	Derivatives	Deriv. m.p., °C.	Deriv., formula	Nitrogen, % Calcd.	Found
C_6H_5–[a]	129–130	3	67	2,4-DNP[b]	211–211.5	$C_{17}H_{12}O_4N_4S$	15.21	15.08
2-C_4H_3S–[c]	133–136	2	63	2,4-DNP	221–222	$C_{15}H_{10}O_4N_4S_2$	14.97	14.91
C_2H_5–	72–74	4[d]	66	2,4-DNP	214–215	$C_{13}H_{12}O_4N_4S$	17.49	17.40
				Semicarb.[e]	186–187	$C_8H_{11}ON_3S$	21.30	21.54
				Thiosemi.[f]	154–154.5	$C_8H_{11}N_3S_2$	19.70	19.61
n-C_3H_7–	80–83	4[g]	62	2,4-DNP	166–166.5	$C_{14}H_{14}O_4N_4S$	C, 50.29	C, 50.41
							H, 4.22	H, 4.04
							16.76	16.80
				Semicarb.	170–171	$C_9H_{13}ON_3S$	19.89	19.70
n-C_4H_9–	80–81	2[h]	56	2,4-DNP	164–165	$C_{15}H_{16}O_4N_4S$	16.09	15.79
				Semicarb.	133–133.5	$C_{10}H_{15}ON_3S$	C, 53.30	C, 53.39
							H, 6.71	H, 6.53
							18.65	18.01

[a] A solid, m.p. 63–64° (ref. 19). *Anal.* Calcd. for $C_{11}H_8OS$: S, 17.03. Found: S, 17.33. [b] 2,4-Dinitrophenylhydrazone. [c] A solid, m.p. 63°. *Anal.* Calcd. for $C_9H_6OS_2$: S, 33.01. Found: S, 33.42. [d] d^{20}_{20} 1.1187, $n^{18}D$ 1.5471. [e] Semicarbazone. [f] Thiosemicarbazone prepared by W. L. Archer. [g] d^{20}_{20} 1.1433, $n^{19}D$ 1.5268. [h] d^{20}_{20} 1.0968, $n^{23}D$ 1.5258.

thenoyl chloride can be caused to react with other aromatic compounds under Friedel–Crafts conditions. In this way, we were able to synthesize 3-(2′-theno)-thienone (I, R = 2-C_4H_3S) in satisfactory yields from thiophene, using stannic chloride in benzene solution. The corresponding reaction between 3-thenoyl chloride and benzene could not be effected. Stannic chloride is not sufficiently active as a Friedel–Crafts catalyst to bring about substitution of the unsubstituted benzene ring. Aluminum chloride caused the formation of a tarry resin, with the evolution of hydrogen sulfide, even though the catalyst was added slowly to the thenoyl chloride in excess benzene. Although aluminum chloride has been used successfully in the thiophene series,[21] in all such cases a deactivating substituent is introduced into the 2-position. In the present case, the product contains a thiophene ring unsubstituted in the 2- and 5-positions, which could polymerize or decompose in the presence of aluminum chloride, or react further with acid chloride, thus accounting for the tars obtained.

The synthesis of 3-benzothienone (I, R = C_6H_5) was accomplished eventually in satisfactory yields by two different methods. The reaction of 3-thenonitrile, which was obtained readily from 3-thenaldehyde, with the phenyl Grignard reagent, or the reaction of 3-thenoyl chloride with diphenylcadmium, gave the same ketone.[19]

Since the reaction of 3-thenoyl chloride with dimethylcadmium already had proved to be an excellent method for the synthesis of 3-acetothienone,[18] this general method was used in the



I

R = C_2H_5, C_3H_7-n, C_4H_9-n, C_6H_5

preparation of 3-thienyl alkyl ketones listed in Table I. In these preparations, the precautions and techniques described by Cason[22] were followed rather closely. In the initial preparation of the Grignard, excess halide was used to ensure complete consumption of magnesium, and anhydrous cadmium chloride was added immediately. The organocadmium syntheses went to completion in 30 to 60 minutes, as shown by a negative test for Grignard reagent performed in every case. In initial experiments, the reaction of 3-thenoyl chloride with dialkylcadmium compounds was carried out in ether, but later it was found that replacing the ether with benzene markedly increased the yields, an effect already noted by Cason.[22] It should be noted that in changing the solvent, it was necessary to fractionally distil the ether, since the lower molecular weight dialkylcadmium compounds are volatile and highly flammable. Although Cason[22] reports that the maximum useful ratio of alkyl halide to acid chloride is 1.25, in these experiments we have used a ratio of about 3, in order to ensure complete consumption of the more expensive acid chloride. Again, although one to three hours was reported as adequate for completion of the reaction,[22] we found that four to eight hours refluxing in benzene improved the yields slightly. In no case, however, were the yields as high (88%) as previously had been obtained using dimethylcadmium.[18]

The liquid 3-thienones were more unstable to heat and light than phenones, and therefore were used soon in the preparation of the hydantoins. They were analyzed as their 2,4-dinitrophenylhydrazones and semicarbazones. Because of the relatively high activity of 2-propanothienone thiosemicarbazone against the tubercle bacillus *in vitro*,[23] a large sample of 3-propanothienone thiosemicarbazone was prepared and submitted to Dr. R. L. Thompson, of the Sterling–Winthrop Research Institute, for evaluation as an anti-viral and antibiotic agent.[24]

The synthesis of 3-(2′-theno)-thienone supplies

(21) Reference 20, pp. 321–325.

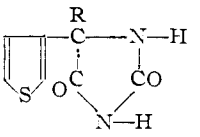
(22) J. Cason, THIS JOURNAL, **68**, 2078 (1946).

(23) F. E. Anderson, C. J. Duca and J. V. Scudi, *ibid.*, **73**, 4967 (1951).

(24) E. Campaigne, P. A. Monroe, B. Arnwine and W. L. Archer, *ibid.*, **75**, 988 (1953).

TABLE II

5-SUBSTITUTED-5-(3-THIENYL)-HYDANTOINS

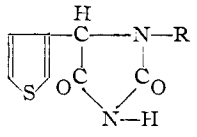


R	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found	Sulfur, % Calcd.	Found
CH_3–	152–153	40	$C_8H_8O_2N_2S$	14.28	14.65	16.35	16.42
C_2H_5–	179–180	64	$C_9H_{10}O_2N_2S$	13.32	13.58	15.25	15.18
n-C_3H_7–	214–215	38	$C_{10}H_{12}O_2N_2S$	12.50	12.62	14.30	14.63
n-C_4H_9–	247–247.5	34	$C_{11}H_{14}O_2N_2S$	11.76	11.67	13.45	13.61
C_6H_5–	254–254.5	92	$C_{13}H_{10}O_2N_2S$	10.85	10.62	12.41	12.44
2-C_4H_3S–	222.5–223	74[a]	$C_{11}H_8O_2N_2S_2$	10.60	11.08	24.27	24.17

[a] Based on unrecovered ketone.

TABLE III

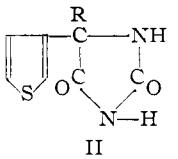
1-SUBSTITUTED-5-(3-THIENYL)-HYDANTOINS



R	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found	Sulfur, % Calcd.	Found
C_2H_5–	159–160	51	$C_9H_{10}O_2N_2S$	13.32	13.56	15.25	15.20
n-C_3H_7–	120–121	66	$C_{10}H_{12}O_2N_2S$	12.50	12.44	14.30	14.23
i-C_3H_7–	128–129	17	$C_{10}H_{12}O_2N_2S$	12.50	12.69	14.30	14.65
n-C_4H_9–	99–100	23	$C_{11}H_{14}O_2N_2S$	11.76	11.66	13.45	13.67
$C_6H_5CH_2$–	221–222	24	$C_{14}H_{12}O_2N_2S$	10.29	10.26	11.77	11.68
CH_2=$CHCH_2$–	140–141	44	$C_{10}H_{10}O_2N_2S$	12.60	12.19	14.43	14.70

the missing third isomer in the dithienyl ketone series. It is interesting to note the orderly increase of 8° in melting point as one goes from 2-thienyl to 3-thienyl substitution in this series of carbonyl derivatives: *i.e.*, 2-(2′-theno)-thienone, 56°; 3-(2′-theno)-thienone, 64°; 3-(3′-theno)-thienone, 72°. This same increment of 8 ± 1° has been observed in the melting point of other carbonyl derivatives as one goes from phenyl → 2-thienyl → 3-thienyl. For example: benzoic acid, 122°; 2-thenoic acid, 130°; 3-thenoic acid, 138°; and benzophenone, 48°; 2-benzothienone, 56°; 3-benzothienone, 64°.

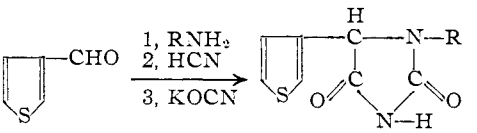
The 5-substituted-5-(3-thienyl)-hydantoins, including the analogs of Nirvanol (II, R = C_2H_5) and Dilantin (II, R = C_6H_5), were prepared from the corresponding 3-thienones by the Bucherer–Bergs synthesis.[25] This involved sealing one part, by molarity, of the ketone with three parts of potassium cyanide and four parts of ammonium carbonate in 60% aqueous ethanol in an autoclave or a large Carius tube, and heating for a period of time at 110°. A reaction time of 12–24 hours was adequate for the preparation of hydantoins from the alkyl 3-thienyl ketones, while 90 hours or more was required for reasonable yields of hydantoins from the aryl 3-thienyl ketones. In view of the observation by Chabrier and Tchoubar[26] that, while 2-thienones gave very poor yields of hydantoins in the Bucherer reaction, 3-thienones were quite satisfactory, the modest yields reported in Table II for several of these reactions are probably not optimum. Indeed, since this work was completed, Spurlock[6] has reported on methods of improving the yields in the 2-thienyl series which probably could be used in the 3-thienyl series to advantage.



R = CH_3, C_2H_5, C_3H_7-n, C_4H_9-n, C_6H_5, 2-C_4H_3S

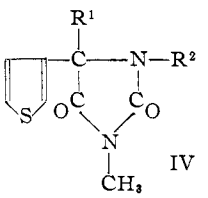
II

The 1-substituted-5-(3-thienyl)-hydantoins (III) were prepared by the method of Long, Miller and Chen.[9] 3-Thenaldehyde was converted to a thenylideneamine, and then, without isolation, hydrogen cyanide was added to form the cyanoamine which, when treated with potassium cyanate in acid solution, was converted to the desired hydantoin. The melting points, yields and analyses of these hydantoins may be found in Table III.



R = C_2H_5, C_3H_7-n, C_3H_7-i, C_4H_9-n, $C_6H_5CH_2$, C_3H_5 III

The anticonvulsant activity of Mesantoin suggested the preparation of some 3-methyl-5-(3-thienyl)-hydantoins of structure IV. Two of these, 3-methyl-5-ethyl-5-(3-thienyl)-hydantoin (IVa) and 1-propyl-3-methyl-5-(3-thienyl)-hydantoin (IVb) were prepared by methylation of the appropriate



a, R^1 = C_2H_5, R^2 = H
b, R^1 = H, R^2 = C_3H_7-n IV

(25) H. Bergs, German Patent 566,094, May 26, 1929; *C. A.*, **27**, 1001 (1933); H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, **141**, 5 (1934).

(26) P. Chabrier and B. Tchoubar, *Compt. rend.*, **220**, 284 (1945).

hydantoin with methyl iodide in alkaline methanol. Although the hydrogen of position 3 in the hydantoins is more acidic and more readily substituted under alkaline conditions, it is probable that when both nitrogens are unsubstituted, as in the preparation of IVa, yields are decreased by some disubstitution.[6] This is illustrated clearly by the quantitative yield obtained on methylation of the hydantoin in which the N_1 is blocked, in the preparation of IVb.

Pharmacological Data.—The anticonvulsant assays have been carried out, using the rat as a test animal, on four of the 5-(3-thienyl)-hydantoins. In each case, a parallel experiment using the phenyl analog of the compound under examination was carried out, in order to get a comparison of activity under as nearly identical conditions as possible. The comparative data are presented in Table IV. Therapeutic ratios were calculated by dividing the toxic $dose_{50}$ by the effective $dose_{50}$ in the electro-shock test.

TABLE IV

TOXICITY AND ANTICONVULSANT ACTIVITY OF CERTAIN 5-(3-THIENYL)-HYDANTOINS

No.	Compound	Time of test, hr.	Route of admin.	TD_{50}[a] mg./kg.	ED_{50},[a] M.E.-S.[b]	mg./kg. Metrazole[c]	Protective index[d]
1	II, R = C_2H_5	2	s.c.	250	20	175	12
2	Nirvanol	3	oral	119	10	62	12
3	II, R = C_6H_5	0.5	s.c.	250	10	>300	25
4	Dilantin	0.5	s.c.	125	9.0	...	14
5	II, R = 2-C_4H_3S	1	s.c.	100	9	>200	11
6	Thiantoin	1	s.c.	75	18.5	...	4
7	IVa	2	s.c.	100	22	>125	5
8	Mesantoin	2	oral	143	10	105	14

[a] Approximate values. [b] Electroshock 150 m.a.; 0.2 sec. [c] Metrazole, 70 mg./kg. s.c. [d] TD_{50}/ED_{50}(M.E.S.)

Based on the limited data above, several generalizations may be made. In the hydantoin series, substitution of a 3-thienyl group for a phenyl group in the 5-position usually decreases toxicity (compare 1 and 2, 3 and 4, 5 and 6). The effect on activity of this substitution is unpredictable; it may decrease (1 *vs.* 2), be equal (3 *vs.* 4) or increase (5 *vs.* 6). However, because of the decrease in toxicity, a favorable shift in the therapeutic ratio usually is observed. Methylation of N^3 in the 3-thienylhydantoin series increased toxicity with little alteration of activity (compare 1 and 7). The opposite effect is seen in the phenyl pair (2 and 8). Spurlock[6] noted that in the 2-thienylhydantoin series, N-alkylation reduced activity, but did not report toxicity data. Substitution of 2-thienyl for phenyl served to increase toxicity without much change in activity (compare 5 with 3), while substitution of 3-thienyl for 2-thienyl doubled the activity and at the same time decreased the toxicity by a factor of three (compare 3 with 6).

Acknowledgment.—We are indebted to Dr. L. S. Goodman, of the University of Utah, and the Sterling–Winthrop Research Institute for the pharmacological data presented in Table IV, and to the Sterling–Winthrop Research Institute for the Fellowship in support of this research.

Experimental

3-Thenonitrile.—The reaction of 3-thenaldehyde[27] with hydroxylamine hydrochloride in pyridine and absolute alcohol[28] gave a quantitative yield of 3-thenaldoxime, melting sharply at 113–114°.[17] The oxime, when refluxed with acetic anhydride, gave a 68% yield of 3-thenonitrile (3-cyanothiophene), b.p. 59° at 3 mm., d^{20}_{20} 1.1956, $n^{21}D$ 1.5565. Elpern and Nachod report b.p. 203–205° and $n^{25}D$ 1.5534 for this compound.[29]

3-Benzothienone.—The phenyl Grignard reagent was prepared from 47.1 g. (0.3 mole) of freshly distilled bromobenzene in dry ether. To this solution was added slowly, with stirring, 7.2 g. (0.066 mole) of 3-thenonitrile in 50 ml. of dry ether at such a rate as to keep the solution refluxing gently. After addition was complete, refluxing was maintained for four hours, and the solution allowed to stand overnight. The complex was hydrolyzed by pouring over ice and dilute sulfuric acid, and the ether layer separated. A yellow precipitate which formed during the acid hydrolysis was dissolved in 6 *N* sodium hydroxide, and this oily solution extracted with ether. The two ether extracts were combined, washed with water several times and dried. After removal of ether, the product was distilled, and 6.9 g. (56%) of a heavy oil boiling at 129–130° at 3 mm. was collected. On cooling in a Dry Ice–acetone bath, 3-benzothienone set to a jelly-like mass which gradually crystallized in fine needles when triturated vigorously. It then could be recrystallized from methanol or hexane in white plates, melting at 63–64°.[19] The reaction of diphenylcadmium with 3-thenoyl chloride, by the general method described below, gave this same product in superior yields (see Table I). The 2,4-dinitrophenylhydrazone crystallized from chloroform in orange needles.

3-(2-Theno)-thienone.—Using a modified Friedel–Crafts reaction,[20] a mixture of 8.4 g. (0.1 mole) of freshly distilled thiophene, 7.3 g. (0.05 mole) of freshly prepared 3-thenoyl chloride[18] and 50 ml. of dry benzene was cooled to 0° and 13 g. (0.05 mole) of freshly distilled stannic chloride was added dropwise with stirring during the course of 30 minutes. The mixture then was stirred for three hours at room temperature, and finally refluxed for three hours. After decomposing the complex over ice and hydrochloric acid, the benzene solution was worked up in the usual manner. After removal of solvent, a heavy oil which solidified in the receiver was collected from 133–136° at 2 mm. The product was recrystallized from hexane in white needles which melted sharply at 63° and weighed 6.1 g. When mixed with 3-benzothienone, the melting point was depressed to 41–59°. The 2,4-dinitrophenylhydrazone was recrystallized from chloroform in red needles.

3-Acylthiophenes.—The 3-acylthiophenes and 3-benzothienone described in Table I were prepared from 3-thenoyl chloride and the organocadmium reagents, using techniques and precautions suggested by Cason.[22] The preparation of 3-propanothienone will serve to illustrate the general method. Ethyl Grignard reagent was prepared by allowing an excess (65.4 g., 0.60 mole) of freshly distilled ethyl bromide to react with 10.0 g. (0.412 mole) of magnesium turnings in dry ether. After the magnesium had dissolved, the solution was cooled in an ice-bath and 40 g. (0.22 mole) of Mallinckrodt "Anhydrous Analytical Reagent" grade cadmium chloride was stirred into the solution at a rate slow enough to keep the vigorous reaction under control. The ice-bath was then removed and the mixture stirred at room temperature until the Grignard reagent had disappeared (usually about 30 minutes), as evidenced by a negative Gilman test.[31] The ether was distilled through a vertical column until a marked slowing in the rate of distillation showed that most of the ether was gone. Then 125 ml. of dry thiophene-free benzene was added and a further 25–50 ml. of distillate was collected. Another 375 ml. of benzene then was added, the column replaced by a reflux condenser, and the solution heated to boiling. The heating unit

(27) E. Campaigne, R. C. Bourgeois and W. C. McCarthy, *Org. Syntheses*, **33**, 93 (1953).

(28) *Cf.* W. E. Bachmann and C. H. Boatner, THIS JOURNAL, **58**, 2097 (1936).

(29) Which is incorrectly named "3-thienylnitrile," B. Elpern and F. C. Nachod, *ibid.*, **72**, 3379 (1950).

(30) J. Johnson and G. E. May, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 8.

(31) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

was removed, and 20.0 g. (0.137 mole) of 3-thenoyl chloride in 100 ml. of dry benzene was added, with stirring, at such a rate as to keep the solution refluxing. When addition was complete, the solution was refluxed for eight hours longer, during which hard lumps of complex settled out of the solution. After standing overnight, the solution was cooled in an ice-bath, and the complex hydrolyzed by the cautious addition of chipped ice to the stirred mixture. Finally dilute sulfuric acid was added until the basic salts were dissolved. The benzene layer was separated, combined with benzene washings of the aqueous layer, and, after several washings with water and aqueous bicarbonate, dried.

After removal of solvent, the product was distilled at reduced pressure, and 12.5 g. of a colorless to pale yellow oil was obtained. The 2,4-dinitrophenylhydrazone was obtained as red needles, and the semicarbazone as white needles, by the usual procedures. The thiosemicarbazone was prepared in nearly quantitative yield by refluxing an equimolar mixture of thiosemicarbazide and 3-propanothienone in 95% ethanol containing a little glacial acetic acid.[24] The yields, physical constants and analyses of the various 3-thienones and their derivatives are reported in Table I.

5-Ethyl-5-(3-thienyl)-hydantoin.—A solution of 7.0 g. (0.05 mole) of 3-propanothienone in 100 ml. of 60% aqueous ethanol was placed in a 600-ml. Pyrex liner of an autoclave, and 9.8 g. (0.15 mole) of potassium cyanide and 19.2 g. (0.20 mole) of ammonium carbonate were added. The autoclave was sealed, and the temperature maintained at 110 ± 2° for 16 hours by means of an electric heating jacket. After cooling, the autoclave was opened under the hood, and the light brown jellied reaction mixture was transferred into 250 ml. of cold water. The solution was acidified (*Caution:* hydrogen cyanide is liberated) and the precipitate collected and redissolved in 150 ml. of 5% sodium hydroxide forming a dark red solution. Upon acidification with dilute hydrochloric acid, the solution became straw-yellow, and a yellowish-brown solid precipitated. It was dissolved in hot dilute acetic acid, decolorized with Nuchar, and recrystallized a second time in dilute acetic acid to give 7.2 g. of pale yellow needles. In the same way, 3-acetothienone, prepared as previously described,[7] was converted to 5-methyl-5-(3-thienyl)-hydantoin, and 3-butanothienone yielded 5-(1-propyl)-5-(3-thienyl)-hydantoin. The properties of these hydantoins are listed in Table II.

5-Phenyl-5-(3-thienyl)-hydantoin.—A solution of 9.4 g. (0.05 mole) of 3-benzothienone in 60 ml. of 95% ethanol was placed in a large Carius tube, and a mixture of 9.8 g. (0.15 mole) of potassium cyanide and 19.2 g. (0.20 mole) of ammonium carbonate suspended in 40 ml. of water was added. The tube was sealed and placed in a Carius furnace maintained at 110° for 105–110 hours. When cooled, the tube was broken open, and the product worked up as described above for 5-ethyl-5-(3-thienyl)-hydantoin, to give 11.9 g. of white crystals. In a similar reaction with 3-(2′-theno)-thienone which was allowed to react for 90 hours, it was necessary to extract the alkaline solution with ether to remove an oily impurity, from which 51% of unreacted ketone was recovered. The yield of 5-(2-thienyl)-5-(3-thienyl)-hydantoin was only 34% of starting ketone. The reaction with 3-pentanothienone also was carried out in a Carius tube, but there was little inprovement in the yield over the reaction carried out in the autoclave. Table II lists the properties of the hydantoins prepared by this method also.

1-Alkyl-5-(3-thienyl)-hydantoins.—These hydantoins are reported in Table III. The preparation of 1-propyl-5-(3-thienyl)-hydantoin is typical of this series. A solution of N-(3-thenylidene)-propylamine was prepared by mixing, in a small flask equipped with stirrer, reflux condenser and dropping funnel, 10 ml. of water and 11.2 g. (0.1 mole) of 3-thenaldehyde, and adding dropwise 6.3 g. (0.01 mole) of propylamine[32] over a period of about 15 minutes. Stirring was continued for one hour, until the warm solution had cooled to room temperature. The flask then was immersed in an ice-bath and the mixture cooled to 0°. In another flask, a solution of hydrogen cyanide was prepared by adding in portions 7.6 g. (0.12 mole) of potassium cyanide to 42 ml. of ice-cold 80% aqueous acetic acid. The mixture was stirred vigorously and cooled during the addition, to avoid loss of hydrogen cyanide.

When the hydrogen cyanide solution was again cooled to 0°, the cold solution of N-(3-thenylidene)-propylamine was added at a rapid rate with stirring. The mixture was stirred and cooled to −5° in an ice–salt-bath, and 9.0 g. (0.11 mole) of potassium cyanate was added rapidly. There was a slight rise in temperature during this addition. Stirring was continued at 0° for one hour, and then 33 ml. of concentrated hydrochloric acid was added dropwise, keeping the solution below 15°. Stirring was continued for one-half hour, and then the mixture was heated on a steam-bath for one-half hour. When this mixture was poured over 100 g. of ice, a heavy yellow oil separated and formed a solid cake. The solid product was dissolved in 5% sodium hydroxide, treated with Norite, and reprecipitated with hydrochloric acid. The precipitate was crystallized from dilute acetic acid in pale yellow needles weighing 14.9 g.

3-Methyl-5-ethyl-5-(3-thienyl)-hydantoin (IVa).—The methylations were carried out as described by Siemonsen.[33]

A solution of 4.1 g. (0.02 mole) of 5-ethyl-5-(3-thienyl)-hydantoin, 1.1 g. (0.02 mole) of potassium hydroxide pellets and 2.8 g. (0.02 mole) of methyl iodide in 50 ml. of methanol was refluxed for four hours. The methanol and excess methyl iodide were evaporated, and the yellow solid residue extracted with several portions of hot methanol. The yellow crystals which were collected from the cooled methanol extracts were recrystallized from dilute acetic acid to give white needles which melted at 112–113° and weighed 1.3 g. (30%).

Anal. Calcd. for $C_{10}H_{12}O_2N_2S$: N, 12.50; S, 14.30. Found: N, 12.54; S, 14.13.

1-Propyl-3-methyl-5-(3-thienyl)-hydantoin (IVb).—A solution containing 0.02 mole each of 1-propyl-5-(3-thienyl)-hydantoin, potassium hydroxide and methyl iodide in 50 ml. of methanol was refluxed for two hours. The product was crystallized once from methanol and once from hexane to yield 4.8 g. (100%) of white crystals melting at 82–83°.

Anal. Calcd. for $C_{11}H_{14}O_2N_2S$: N, 11.76; S, 13.45. Found: N, 11.17; S, 13.59.

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(32) In the preparation of 1-ethyl-5-(3-thienyl)-hydantoin, 29 ml. of a 33% solution of ethylamine in water, containing 0.21 mole of ethylamine, was used with 0.1 mole of aldehyde; in all other cases the pure amine was used in the proportions indicated.

(33) L. Siemonsen, *Ann.*, **333**, 113 (1904).