addition to electrostatic effects, structural characteristics doubtlessly are of significance. This phase of the problem is now under investigation.

NEW YORK 21, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTH TEXAS STATE COLLEGE]

Hydantoins as Anticonvulsants. I. 5-R-5-(2-Thienyl)-hydantoins[1]

BY JAMES J. SPURLOCK

RECEIVED AUGUST 11, 1952

The synthesis of nineteen 5-substituted-5-(2-thienyl)-hydantoins and nine 3-alkyl- or 1,3-dialkyl-5-substituted-5-(2-thienyl)-hydantoins is described in this work. The compounds were tested elsewhere for anticonvulsant activity and the results are reported. A few of the compounds were of the same order of activity as 5,5-diphenylhydantoin (dillantin). N-Alkylation reduced anticonvulsant activity in every case.

There has been in progress in this Laboratory during the past several years a program which has for its purpose the study of the effect of varied substitution of the hydantoin nucleus on its anticonvulsant activity. This paper is the first of a series which describes the synthesis and gives the results of testing elsewhere of these compounds.

At the St. Louis Meeting of the American Chemical Society in 1941, there were described five examples of 5-substituted-5-(2-thienyl)-hydantoins. These and certain others were patented in 1945.[2] In 1945, Chabrier and Tchoubar[3] reported the synthesis of 5-ethyl-5-(2,5-dimethyl-3-thienyl)-hydantoin, 5-methyl-5-(2,5-dimethyl-3-thienyl)-hydantoin and 5-methyl-5-(5-methyl-2-thienyl)-hydantoin. The latter compound was reported in low yield (5–10%), and these authors report that under the conditions used they were unable to synthesize 5-methyl-5-(2-thienyl)-hydantoin. In 1949, Long and Miller reported the synthesis of a series of 1-alkyl- or/and -aryl-5-(2-thienyl)-hydantoins.[4] In 1949, also, Bywater and Coleman[5] were issued a patent relating to 5,5-di-(2-thienyl)-hydantoin.

The compounds described in the present work were prepared by a modification of the method of Bucherer[6] in which the appropriate ketone is heated with ammonium carbonate and potassium cyanide

TABLE I

ALKYL 2-THIENYL KETONES, R(C_4H_3S)CO

R	B.p., °C. at atm. press.	d^{20}_4	$n^{20}D$	Yield, %
Methyl[a]	214	1.1711	1.5652	63
Ethyl[b]	227	1.1305	1.5533	70
n-Propyl[c]	240	1.0941	1.5434	74
i-Propyl[d]	228	1.0894	1.5405	72
n-Butyl[e]	258	1.0664	1.5357	76
i-Butyl[f]	245	1.0619	1.5330	73
n-Amyl[g,h]	275	1.0473	1.5301	80
i-Amyl[i]	267	1.0419	1.5273	83

[a] A. Peter, *Ber.*, **17**, 2643 (1884). [b] K. Krekeler, *ibid.*, **19**, 677 (1886). [c] W. Steinkopf and I. Shubart, *Ann.*, **424**, 10 (1920); H. Scheibler and F. Rettig, *Ber.*, **59**, 1194 (1926), report d^{20}_{20} 1.0730, $n^{20}D$ 1.52418. [d] Krekeler, ref. *b*, p. 675. [e] P. Cagniant and A. Deluzarche, *Compt. rend.*, **223**, 1149 (1946). [f] Steinkopf and Shubart, ref. *c*, p. 11. [g] Cagniant and Deluzarche, *Compt. rend.*, **225**, 456 (1947), report d^{17}_4 1.0463, $n^{17}D$ 1.5299; E. Campaigne and J. L. Diedrich, THIS JOURNAL, **70**, 392 (1948), report d^{20}_4 1.065, $n^{20}D$ 1.5301. [h] Fifty-five per cent. of the anticonvulsant activity of dillantin. Electroshock test in cats; equal doses of 50 mg./kg. [i] Calcd. for $C_{10}H_{14}OS$: S, 17.59. Found: S, 17.45.

TABLE II

ARYL, ARALKYL AND CYCLOALKYL 2-THIENYL KETONES, RR'CO

R	R'	M.p., °C.	Yield, %	Anti-convulsant activity[m]
Phenyl	2-Thienyl[a]	55.5–56	86	30
Cyclohexyl	2-Thienyl[b]	43–43.5	88	
4-Methyl-phenyl	2-Thienyl[c]	75–76	93	0
Benzyl	2-Thienyl[d]	49–50	86	20
2-Phenyl-ethyl	2-Thienyl[e]	45–45.5	88	
Benzhydryl	2-Thienyl[f]	134.5–136	55	30
Phenyl	5-Methyl-2-thienyl[g,h]	Oil	54	
Phenyl	4-Methyl-2-thienyl[i]	91–92	81	
4-Fluoro-phenyl	2-Thienyl[j]	95.5–96	45	
Phenyl	5-Chloro-2-thienyl[k]	48.5–49.5	76	
Phenyl	5-Bromo-2-thienyl[l]	75.5–76	76	

[a] A. Comey, *Ber.* **17**, 790 (1884). [b] B.p. 142–144° (4 mm.). Calcd. for $C_{11}H_{14}OS$: S, 16.50. Found: S, 16.48. [c] W. Steinkopf and M. Bauermeister, *Ann.*, **403**, 71 (1914). [d] P. Cagniant and A. Deluzarche, *Compt. rend.*, **223**, 1150 (1946), report m.p. 44.5°. [e] B.p. 189–191° (9 mm.). Calcd. for $C_{13}H_{12}OS$: S, 14.80. Found: S, 14.69. [f] Calcd. for $C_{18}H_{14}OS$: C, 77.67; H, 5.07. Found: C, 77.74; H, 5.22. [g] B.p. 142–144° (2.5 mm.). [h] J. Volhard, *Ann.*, **267**, 182 (1892), reports m.p. 124°. Ernst, *Ber.*, **19**, 3280 (1886), reports the substance is an oil. [i] W. Steinkopf and H. Jacob, *Ann.*, **515**, 281 (1935). [j] B.p. 142–145° (4 mm.). Calcd. for $C_{11}H_7OSF$: C, 64.06; H, 3.42. Found: C, 64.41; H, 3.76. [k] B.p. 153–155° (4 mm.). Calcd. for $C_{11}H_7OSCl$: S, 14.37. Found: S, 14.41. [l] A. W. Weitkamp and C. S. Hamilton, THIS JOURNAL, **59**, 2701 (1937). [m] Per cent. of activity of dillantin. Equal doses of 50 mg./kg. in cats by electroshock method.

(1) Presented at the 117th Meeting of the American Chemical Society at Philadelphia, Pa., 1950.

(2) James J. Spurlock, U. S. Patent 2,366,221, Jan. 2, 1945

(3) P. Chabrier and B. Tchoubar, *Compt. rend.*, **220**, 284 (1945); see also P. Chabrier, B. Tchoubar and S. LeTellier-Dupre, *Bull. soc. chim.*, 332 (1946).

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

(5) W. G. Bywater and W. R. Coleman, U. S. Patent 2,468,168, April 26, 1949.

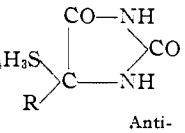
(6) H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

in a solvent such as dilute alcohol. It was found necessary to heat the reaction mixture at a temperature of about 110° under pressure, and to add a total of about 3 moles of potassium cyanide in two portions in order to obtain satisfactory yields. The ketones used in this preparation were prepared by the Friedel–Crafts reaction using an acid chloride and thiophene or a substituted thiophene, with anhydrous stannic chloride as the condensing agent. The N-alkylated hydantoins were prepared by the reaction of an alkyl sulfate with the sodium hydantoinate in absolute methanol or ethanol.

The anticonvulsant tests were carried out in the Pharmacology Laboratories of the Eli Lilly Company by Mr. E. E. Swanson and co-workers, using the electroshock method with cats, with dillantin as the standard.

The author wishes to acknowledge the helpful suggestions of the late H. A. Shonle and generous financial support of the Eli Lilly Company.

TABLE III

5-ALKYL-5-(2-THIENYL)-HYDANTOINS 

R	M.p., °C.	Nitrogen, % Calcd.	Found	Yield, %	Anti-convulsant activity[b]
Methyl	138.5–140	14.32	14.49	35	33
Ethyl	177–177.5	13.33	13.39	76	60[c]
n-Propyl	178.5–179	12.49	12.28	85	55
i-Propyl	196–197 (188)[a]	12.49	12.52	79	50
n-Butyl	230–231	11.76	11.91	88	88
i-Butyl	155–156.5	11.76	11.39	73	80
n-Amyl	154–154.5	11.11	11.10	82	50
i-Amyl	159–160	11.11	11.21	93	50

[a] M.p. 188° with rapid heating. If heated very slowly or if maintained at a temperature just below 188° for a few minutes m.p. 196–197°. [b] Per cent. of activity of dillantin. Equal doses of 50 mg./kg. in cats using electroshock test. [c] 5-Ethyl-5-phenylhydantoin = 100.

Densities were determined using a pycnometer of about 1.4-ml. capacity. The yields reported are those of the crude material as obtained from the reaction mixture, if a solid, or with a boiling range of 2–4° if a liquid. Sulfur analyses were carried out using the Carius method; nitrogen analyses were carried out by the micro Dumas method.

2-Thienyl Ketones.—The 2-thienyl ketones were prepared by essentially the method described in reference 7. The materials were first distilled, and then if solids, were recrystallized from hexane or petroleum ether. The properties, yields and other data for the ketones are summarized in Tables I and II.

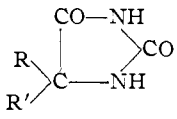
5-Substituted-5-(2-thienyl)-hydantoins.—The preparation of 5-methyl-5-(2-thienyl)-hydantoin which follows is typical of the preparation of the remainder of the compounds.

Three and seventy-nine hundredths grams (0.03 mole) of methyl 2-thienyl ketone dissolved in 75 ml. of ethanol is added to a solution of 3.25 g. (0.045 mole) of 90% potassium cyanide and 10.2 g. (0.09 mole) of ammonium carbonate in 75 ml. of water. The mixture is placed in a small autoclave and heated for about 18 hours at 110°. There is then put in an additional 3.25 g. (0.045 mole) of potassium cyanide and 3 g. (0.026 mole) of ammonium carbonate and the heating is continued for an additional 18 hours at the same temperature. The reaction mixture is removed and about half the liquid evaporated on a steam-bath. The mixture is cooled, acidified with hydrochloric acid and extracted with two 50-ml. portions of ether. The ether extracts are combined and shaken with two 25-ml. portions of 5% NaOH solution. On acidification of the aqueous extracts the product separates as an oil which soon solidifies. The yield of crude material is 3.65 g. or 62%. After recrystallization from dilute alcohol the product melts at 138.5–140°. By evaporation of the ether solution there is obtained about 1.2 g. of unreacted ketone.

The properties, yields and analytical data for the 5-substituted-5-(2-thienyl)-hydantoins are summarized in Tables III and IV.

3-Alkyl-5-substituted-5-(2-thienyl)-hydantoins.—The preparation of the 3-alkyl derivatives is substantially the same as the following preparation of 3,5-diethyl-5-(2-thienyl)-hydantoin. Eighty-one hundredths gram (0.035 mole) of sodium is dissolved in 150 ml. of absolute ethanol contained in a 3-necked flask fitted with a mercury-sealed stirrer and a condenser protected with a drying tube. To this solution is added 6.70 g. (0.032 mole) of 5-ethyl-5-(2-thienyl)-hydantoin, followed by 5.4 g. (0.035 mole) of diethyl sulfate. The mixture is then refluxed until it becomes acidic. The alcohol is evaporated on a steam-bath, a small amount of water is added, and the gummy residue is dissolved in about 100 ml. of ether. The ether solution is extracted with 5% Na_2CO_3 solution in 25-ml. portions until acidification produces no precipitate. The total material

TABLE IV

5-ARYL-, ARALKYL- AND CYCLOALKYL-5-(2-THIENYL)-HYDANTOINS 

R	R′	M.p., °C.	Nitrogen, % Calcd.	Found	Yield, %	Anticonvulsant activity[a]
Phenyl	2-Thienyl	256–257	10.85	10.78	56	110
Cyclohexyl	2-Thienyl	244–245	10.60	10.80	71	35
p-Tolyl	2-Thienyl	224–225	10.29	10.07	26	0
Benzyl	2-Thienyl	185–186	10.29	10.30	56	50
2-Phenylethyl	2-Thienyl	183–184	9.79	9.61	93	15
Benzhydryl	2-Thienyl	259–260	8.04	8.18	20	15
Phenyl	5-Methyl-2-thienyl	202.5–203.5	10.29	10.35	41	20[b]
Phenyl	4-Methyl-2-thienyl	249.5–251.5	10.29	10.33	35	0[b]
4-Fluorophenyl	2-Thienyl	227.5–229	10.14	10.34	8	40[b]
Phenyl	5-Chloro-2-thienyl	219–220	9.57	9.64	39	50[b]
Phenyl	5-Bromo-2-thienyl	212.5–213.5	8.31	8.35	25	0[b]

[a] Per cent. of activity of dillantin. Equal doses of 50 mg./kg. in cats using electroshock test. [b] Inactive using the metrazole test with rats.

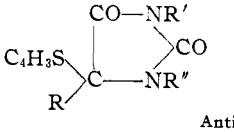
Experimental

All melting points and boiling points are corrected. The boiling points unless otherwise specified were determined at about 745 mm. pressure by distilling a purified sample.

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8.

TABLE V

N-ALKYL-5-SUBSTITUTED-5-(2-THIENYL)-HYDANTOINS



R	R'	R''	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found	Anticonvulsant activity[a]
C_2H_5	CH_3	H	70	140.8–141.1	12.49	12.36	0
C_2H_5	C_2H_5	H	47	109.5–110	11.76	12.04	0
n-C_4H_9	CH_3	H	100	145–146	11.11	11.02	0
n-C_4H_9	C_2H_5	H	70	90.5–91	10.52	10.27	0
C_6H_{11}	CH_3	H	95	198–199	10.07	10.03	25
C_6H_5	CH_3	H	80	155–155.5	10.28	10.13	0
C_6H_5	C_2H_5	H	75	116–117	9.79	9.72	0
C_6H_5	CH_3	CH_3	12	139–140	9.79	9.76	50
2-C_4H_3S	CH_3	H	78	165–166.5	10.07	10.10	0

[a] Per cent. of activity of dillantin. Equal doses of 50 mg./kg. by mouth in cats using electroshock test.

obtained in this fashion weighs 3.4 g. and consists of impure 5-ethyl-5-(2-thienyl)-hydantoin. The ether solution is evaporated giving 3.6 g. of crude product, a yield of 47%. After two recrystallizations from dilute alcohol the compound melts at 109.5–110°

The 3-alkyl-5-substituted-5-(2-thienyl)-hydantoins are soluble in 5% NaOH solution. 1,3-Dimethyl-5-phenyl-5-(2-thienyl)-hydantoin is obtained as a co-product from the preparation of 3-methyl-5-phenyl-5-(2-thienyl)-hydantoin by extracting the ether solution of the crude reaction product with 5% Na_2CO_3 solution and 5% NaOH solution successively. The Na_2CO_3 solution contains a trace of unreacted 5-phenyl-5-(2-thienyl)-hydantoin; the NaOH solution contains 3-methyl-5-phenyl-5-(2-thienyl)-hydantoin; and from the ether solution by evaporation there is obtained a small amount (12%) of 1,3-dimethyl-5-phenyl-5-(2-thienyl)-hydantoin. The melting points, yields and other data for the 3-alkyl-5-substituted-5-(2-thienyl)-hydantoins are shown in Table V.

DENTON, TEXAS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Pyridazine Derivatives. I. Some Amebacidal 3-Pyridazones

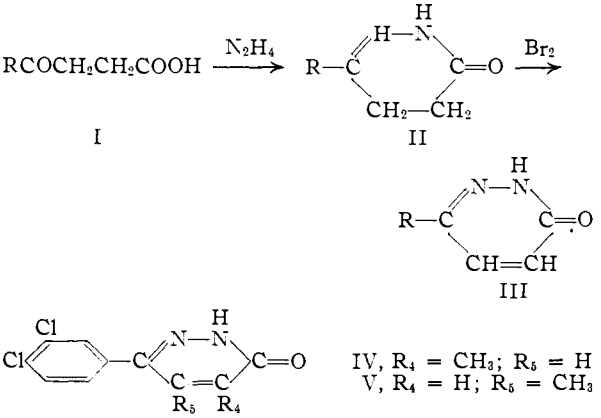
BY EDGAR A. STECK, R. PAULINE BRUNDAGE AND LYNN T. FLETCHER

RECEIVED OCTOBER 15, 1952

The investigation of a series of 6-substituted 4,5-dihydro-3-pyridazones and related 3-pyridazones led to the preparation of 6-(3,4-dichlorophenyl)-3-pyridazone, a new type compound to show amebacidal activity (hamster test).

Pyridazine derivatives do not appear to occur in natural products, and also have been relatively neglected in the investigation of potential pharmaceuticals. Some pyridazines have been examined for activity against sporozoan (SN[1] 416, 497, 498, 5388, 10959, 11065 and 11066) and flagellate[2] parasites, but not for antiamebic activity. The present phase of our work has centered about the preparation of 6-(4-halophenyl)-3-pyridazones for study as amebacides; details concerning the testing of the compounds will be reported elsewhere.

The requisite 6-substituted 3-pyridazones were made by action of hydrazine upon 1,4-dicarbonyl compounds, much after the method first found to yield a pyridazine type.[3] Application of the scheme to 4-substituted-4-oxobutanoic acids (I) to obtain 6-substituted 4,5-dihydro-3-pyridazones (II) and the dehydrogenation of II to the corresponding 3-pyridazones (III) has been well described (*e.g.*, refs. 4–8). The present investigation has led to the synthesis of the 3-pyridazones bearing in position 6 the following groups: 4-chlorophenyl-, 4-bromophenyl-, 5-iodophenyl-, 4-(2,4-dichlorophenyl)- and 4-(3,4-dichlorophenyl)-. There was also prepared from appropriate oxobutanoic acids, the compounds (IV) and (V) as examples of 4/5-alkyl-6-(3,4-dichlorophenyl)-3-pyridazones. When screened for amebacidal activity in the hamster (*Cricetus auratus*),[9] the most effective of the highly insoluble 3-pyridazones was 6-(3,4-dichlorophenyl)-3-pyridazone. It appears that this type of intestinal amebacide may exert its action by achieving useful concentration in the intestinal lumen through low solubility and/or retarded absorption (*cf.* refs. 10a, 10b).



I II III

IV, $R_4 = CH_3$; $R_5 = H$
V, $R_4 = H$; $R_5 = CH_3$

In the present work, the ketonic acids of structure (I) were made by interaction of aromatic types with succinic anhydride under Friedel–Crafts conditions.[11] The greater number of these intermediates were known (the 4-(4-chlorophenyl)-, 4-(4-bromophenyl)- and 4-(4-iodophenyl)-4-oxo-

(1) All compounds designated SN (Survey Number) have been tabulated, together with antimalarial activities, in the monograph, "Antimalarial Drugs, 1941–1945" (F. Y. Wiselogle, editor), Edwards Bros., Ann Arbor, Mich., 1946.

(2) E. Walton, British Patent 573,770.

(3) L. Knorr, *Ber.*, **18**, 305 (1885).

(4) T. Curtius, *J. prakt. Chem.*, [2] **50**, 522 (1894).

(5) R. von Rothenburg, *ibid.*, [2] **51**, 141 (1895).

(6) R. Fittig, *Ann.*, **299**, 16 (1898).

(7) S. Gabriel and J. Colman, *Ber.*, **32**, 395 (1899).

(8) O. Poppenberg, *ibid.*, **34**, 3257 (1901).

(9) E. W. Dennis, D. A. Berberian and S. Hansen, *Am. J. Trop. Med.*, **29**, 683 (1949).

(10) (a) N. J. Conan, Jr., J. A. Head and A. E. Brewer, *Trans. Roy. Soc. Trop. Med. Hyg.*, **43**, 659 (1950); (b) N. J. Conan, Jr., *Am. J. Trop. Med.*, **31**, 18 (1951).

(11) E. Berliner, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., p. 229.