tracted with 1 *N* hydrochloric acid. The neutral products, obtained by distillation of the ether, weighed 0.77 g., were entirely soluble in cold petroleum ether, and yielded a picrate of melting point 141.5–143.5°, indicating that the material was practically pure 1-methylindole. The alkaline fraction, recovered by making the acid extract alkaline and extracting with ether, weighed 0.90 g. (90% recovery) and yielded a picrate of melting point 135.5–137.5°. Two recrystallizations from 95% ethanol raised the melting point to 140–141.5°; mixed melting point with the picrate of II, 144–145.5°.

Summary

The sodium salts of ethyl malonate, ethyl cyanoacetate, ethyl cyanomalonate and tricarbethoxymethane have been alkylated with 1-methylgramine methiodide. The highest yield (62.5%) of the substituted malonic acid was obtained by saponifying the alkylation product of tricarbethoxymethane. Decarboxylation of the substituted malonic acid in refluxing pyridine gave a 90% yield of 1-methylindole-3(β)-propionic acid, whose structure was proved by a Curtius degradation.

Ethyl cyanoacetate, ethyl acetamidomalonate, and tricarbethoxymethane have been alkylated with 1-methylgramine. The yields of alkylation products are consistently lower than in the case of corresponding alkylations with gramine.

As a by-product in the alkylations with 1-methylgramine, 1,1′-dimethyl-3,3′-diindolylmethane was obtained. The structure of this product has been proved by unequivocal synthesis. The same product was obtained from methylindole and formaldehyde in the presence of acetic acid, from 1-methylgramine methiodide and aqueous sodium hydroxide or sodium acetate, and from 1-methylgramine hydrochloride and aqueous sodium acetate.

1-Methylgramine was found to be much more stable to heat than gramine.

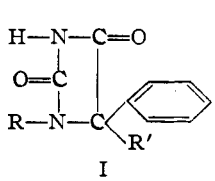
URBANA, ILLINOIS RECEIVED AUGUST 19, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO., DETROIT, MICHIGAN]

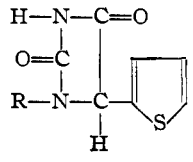
The Preparation of 1-R-5-(2-Thienyl)-hydantoins

BY LOREN M. LONG, C. A. MILLER AND GRAHAM CHEN

We have reported the synthesis and pharmacological activity of a series of 1-R-5-R′-5-phenylhydantoins[1] which may be represented by formula I. As reported in that paper, the more effective compounds in regard to protection against electrically induced convulsions are those in which R represents a short chain hydrocarbon group while R′ represents hydrogen.



I



II

Although our evidence to date does not indicate that the mere substitution of the 2-thienyl group for the phenyl group in physiologically active compounds is likely to lead to derivatives of greatly increased activity, the comparison of such related series is of interest and is sometimes necessary for patent purposes. For these reasons we decided to prepare the 2-thienyl derivatives represented by formula II in which R represents an alkyl, alkenyl, cycloalkyl or aralkyl group.

The only series of thiophene-containing hydantoins previously reported was prepared by Spurlock.[2] This series consists of 5-R-5-(2-thienyl)-hydantoins where R may be an alkyl or a phenyl group. Careful studies[3] recently made employing the electroshock method with cats have indicated that at best these derivatives are equal in activity to the corresponding phenyl compounds and that as a rule they are inferior. Final proof of relative therapeutic effectiveness, however, must await clinical studies.

The compounds summarized in Table I were prepared by the general method outlined in the earlier paper.[1] 2-Thiophenealdehyde was treated with an amine and the resulting thenylidene R-amine was converted to the corresponding aminonitrile by the addition of hydrogen cyanide. Treatment with cyanic acid yields the desired hydantoin. The various intermediates were not isolated. As indicated in Table I, in most instances the yields were inferior to those obtained with benzaldehyde. No attempt was made to improve the method, as sufficient material for testing was obtained in each case.

Pharmacology.—Most of the compounds herein reported have been tested both for inhibition of electrically induced convulsions in cats and metrazol-induced convulsions in rats. The activities listed in Table I indicate that the lower members of the series are the more effective anticonvulsants. This is in accord with the results obtained with the corresponding phenyl derivatives reported in the earlier publication.[1]

In each case, those compounds exhibiting an activity of 4+ when administered to cats in doses of 100 mg./kg. showed a lower activity at 50 mg./kg. Thus, no member of the series is as active as Dilantin.[4]

(1) Long, Miller and Troutman, THIS JOURNAL, **70**, 900 (1948).

(2) Spurlock, U. S. Patent 2,366,221.

(3) Chen and Ensor, unpublished data.

(4) Dilantin, registered trade-mark of Parke, Davis & Co. for 5,5-diphenylhydantoin.

TABLE I

1-R-5-(2-THIENYL)-HYDANTOINS

R	M. p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found	Activity: Electroshock[a]	Activity: Metrazol[b]
Methyl	163–164	38	$C_8H_8N_2O_2S$	14.28	14.29	+	4+/250 mg.
Ethyl	163–165	49	$C_9H_{10}N_2O_2S$	13.33	13.37	4+	3+/50 mg.
Propyl	109–110	47	$C_{10}H_{12}N_2O_2S$	12.49	12.68	4+	3+/125 mg.
Isopropyl	173–174	28	$C_{10}H_{12}N_2O_2S$	12.49	12.47	2+	4+/250 mg.
Allyl	105–106	48	$C_{10}H_{10}N_2O_2S$	12.61	12.38	4+	4+/125 mg.
Butyl	123–125	47	$C_{11}H_{14}N_2O_2S$	11.76	12.01	+	4+/250 mg.
s-Butyl	148–150	7	$C_{11}H_{14}N_2O_2S$	11.76	12.14		
1-Methylbutyl	136–137	14	$C_{12}H_{16}N_2O_2S$	11.11	11.14		+/250 mg.
Cyclohexyl	181–183	2	$C_{13}H_{16}N_2O_2S$	10.60	10.60		
Benzyl	191–193	35	$C_{14}H_{12}N_2O_2S$	10.29	10.29	+	4+/500 mg.
Phenethyl	156–157	61	$C_{15}H_{14}N_2O_2S$	9.79	9.75	+	3+/250 mg.

[a] These results were obtained with an oral dose of 100 mg. for each compound. For a discussion of the method see Putnam and Merritt, *Science*, 85, 525 (1937). [b] An activity of 4+ means that five out of five rats are completely protected against a convulsive dose of metrazol.

Although the activity against metrazol is obtained without evidence of depression, doses at higher levels than those given in Table I induce appreciable hypnosis. Such hypnotic activity is an undesirable characteristic when possessed by potential anticonvulsant compounds.

Experimental

Material.—The 2-thiophenealdehyde employed in the preparation of all of the compounds listed in Table I was obtained from Arapahoe Chemicals, Inc. It was used without further purification. The various amines were supplied by Eastman Kodak Co. or by Sharples Chemicals Inc.

1-Propyl-5-(2-thienyl)-hydantoin.—Except for minor details the preparation of this compound is typical of the series. Aqueous solutions of methylamine and ethylamine were used in preparing the first two members of the series while anhydrous amines were added to aqueous mixtures of 2-thiophenealdehyde in all other preparations. The precipitation of 1-methyl-5-(2-thienyl)-hydantoin from aqueous alkali is best carried out by the addition of hydrochloric acid while carbon dioxide, either gaseous or solid, is completely satisfactory for precipitating the remaining members of the series.

To a mixture of 33.6 g. (0.3 mole) of 2-thiophenealdehyde and 30 ml. of water in a small flask fitted with a mechanical stirrer, a reflux condenser and a dropping funnel was added 18.9 g. (0.32 mole) of propylamine over a period of fifteen minutes. The mixture became quite warm. Stirring was continued for one hour and then the flask was immersed in an ice-bath.

In another flask, equipped with a stirrer and a thermometer, 125 ml. of 80% aqueous acetic acid was cooled to 0°. With slow stirring 22.8 g. (0.35 mole) of potassium cyanide was added in portions so that the temperature remained below 8°. When the addition was complete, stirring was continued until the temperature was 0°.

The cold solution was stirred while the mixture of thenylidene propylamine and water was added at a fairly rapid rate. The temperature remained below 5°. When the addition was complete, the mixture was allowed to cool to −5°. At this point 27 g. (0.32 mole) of potassium cyanate was added rapidly. There was a slight rise in temperature. The mixture was stirred for one-half hour while being cooled and then for an additional half hour at room temperature.

The mixture was again cooled to 0° and 100 ml. of concentrated hydrochloric acid was added dropwise, the temperature remaining below 15°. Stirring was continued for one-half hour followed by heating on a steam-bath for another half hour. The hot mixture was poured into 300 g. of chipped ice. A thick yellow liquid precipitated which solidified after several minutes. The solid product was filtered off and purified by solution in 300 ml. of 5% aqueous sodium hydroxide, charcoaling and reprecipitation with carbon dioxide. Recrystallization from benzene and ligroin resulted in only a slight increase in melting point.

Acknowledgment.—The authors wish to thank Mr. A. W. Spang for the analytical data recorded in Table I and Mr. Charles R. Ensor and Mrs. Isobel G. Clarke for technical assistance in determining the anti-convulsant activity of the compounds reported herein.

Summary

A series of 1-R-5-(2-thienyl)-hydantoins has been prepared and tested for anticonvulsant activity. Those derivatives containing not more than three carbon atoms in the 1-substituent are the more active members of the series against electrically induced and metrazol-induced convulsions.

DETROIT, MICH. RECEIVED SEPTEMBER 27, 1948