cold water and two 5-ml. portions of acetone. The solid weighed 2.4 g. (48%) and melted with decomposition at 213–214° when placed in a bath at 200° and heated at a rate of about 2° per minute. After two recrystallizations from water, it melted at 220–224° with decomposition. This compound contained sulfur but gave no precipitate with acidified silver nitrate solution and produced no color in the diazotization test.

Anal. Calcd. for $C_5H_6O_3N_2S$: N, 16.10. Found: N, 15.98.

One gram of enol salt was suspended in 7.5 ml. of 4 *N* hydrochloric acid. After standing for twenty-four hours, the solid had not dissolved completely. Two ml. of water and a few drops of concentrated hydrochloric acid were added and the mixture was warmed slightly to obtain a clear solution. After standing for another day the solution was evaporated to dryness and the residue was extracted with 30 ml. of ethanol. The extract was diluted with 60 ml. of hexane and on cooling, 0.43 g. of 2-amino-4-hydroxymethylthiazole hydrochloride was obtained, m. p. 157–158°. After two recrystallizations from ethanol the melting point was 162–163°.

Summary

2-Amino-4-chloromethylthiazole (I) was prepared by the reaction of equimolecular quantities α,γ-dichloroacetone and thiourea. S-(2-Amino-4-thiazolylmethyl) isothiourea (II) was obtained when two equivalents of thiourea was used.

2-Amino-4-*t*-aminomethylthiazoles were prepared by the reaction of I with secondary amines and also by the reaction of thiourea with brominated *t*-aminoacetones.

2-Amino-4-hydroxymethylthiazole was obtained by the hydrolysis of I and also through the reaction of α-bromotetronic acid with thiourea.

2- mino-4-alkylmercaptomethylthiazoles were synthesized by treating alkaline solutions of the isothiourea II with alkylating agents.

GLENOLDEN, PENNSYLVANIA RECEIVED MARCH 1, 1946

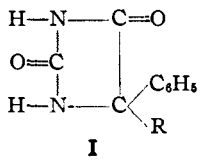
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

5-R-Thiomethyl- and 5-R-Sulfonylmethyl-5-phenylhydantoins

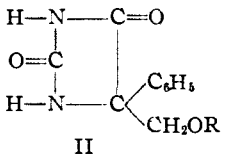
BY LOREN M. LONG

Since the discovery by Putnam and Merritt[1] of the anticonvulsant activity of 5,5-diphenylhydantoin (Dilantin), a large number of compounds have been prepared and tested[2] in an effort to find additional substances of value in the treatment of convulsive seizures. It has been found that numerous substituted hydantoins possess anticonvulsant activity while exhibiting little or no hypnotic activity. In contrast the barbituric acids such as phenobarbital which possess anticonvulsant activity are also powerful hypnotics. It is partly for this reason that so many of the compounds studied have been hydantoins.

Many of the hydantoins which are active have structure (I) where R may be a simple alkyl or a substituted alkyl.

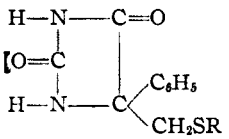


I

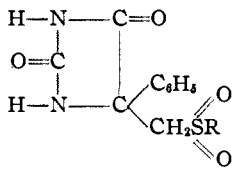


II

One group of compounds prepared by Henze[3,8] which possesses a high degree of activity throughout the series may be represented by formula (II) where R denotes various alkyl groups. Because of this fact and since sulfur containing compounds such as ethyl phenyl sulfide and sulfone have proved to be effective in reducing convulsive seizures,[4] it was considered worth while to prepare a number of compounds represented by (III) and (IV) for anticonvulsant testing.



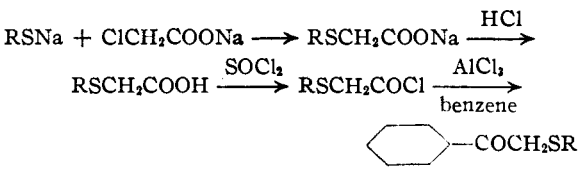
III



IV

The synthesis of these hydantoins necessitated the preparation of a series of α-R-thioacetophenones shown in Table I. Literature investigation revealed that α-*n*-butylthioacetophenone had been prepared by Whitner and Reid.[5] With slight variation their procedure, which involves the reaction of sodium mercaptan with phenacyl chloride, was adequate for the preparation of the entire series.

However, several of the ketones were prepared also by an alternate method illustrated by the reactions



Although the yields obtained in the various steps were good, the over-all yields were lower than those obtained in the first method. The products obtained by the two methods are identical.

Conversion of the ketones to the corresponding hydantoins was carried out by the method of

(1) Putnam and Merritt, *Science*, **85**, 525 (1937).

(2) Merritt and Putnam, *Epilepsia*, **3**, 51 (1945).

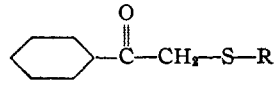
(3) Rigler and Henze, THIS JOURNAL, **58**, 474 (1936).

(4) Merritt, Putnam and Bywater, *Arch. Neurol. Psychiat.*, **54**, 319 (1945).

(5) Whitner and Reid, THIS JOURNAL, **43**, 638 (1921).

TABLE I

α-R-THIOACETOPHENONES,[a]



R	B. p., °C., 2 mm.	$n^{20}D$	Formula	Analyses, %[b] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Methyl[c]	102–104	1.5836	$C_9H_{10}OS$	65.03	65.17	6.06	6.00
Ethyl[c]	106	1.5700	$C_{10}H_{12}OS$	66.63	66.83	6.71	6.99
n-Propyl[c]	120–121	1.5603	$C_{11}H_{14}OS$	68.00	68.06	7.26	7.38
i-Propyl[c]	107	1.5590	$C_{11}H_{14}OS$	68.00	67.96	7.26	7.34
n-Butyl[d]	133	1.5513	$C_{12}H_{16}OS$	69.19	69.12	7.74	7.60
Isobutyl	124–125	1.5486	$C_{12}H_{16}OS$	69.19	69.13	7.74	7.53
n-Amyl	153	1.5457	$C_{13}H_{18}OS$	70.22	69.93	8.16	8.34
n-Hexyl	155	1.5391	$C_{14}H_{20}OS$	71.14	71.00	8.53	8.36
Cyclohexyl	153–155	1.5705	$C_{14}H_{18}OS$	71.75	71.52	7.74	7.89
Phenyl	M. p. = 54°	....	$C_{14}H_{12}OS$	73.67	73.42	5.30	5.42
Benzyl	M. p. = 87°	....	$C_{15}H_{14}OS$	74.34	74.21	5.82	5.85

[a] Yields varied from 85–95%. [b] The analytical data reported in this paper were determined by Arthur W. Spang and Margaret McCarthy Ledyard. [c] Also prepared from the corresponding alkylthioglycolyl chloride, benzene and aluminum chloride. [d] See ref. 5.

TABLE II

5-R-THIOMETHYL-5-PHENYLHYDANTOINS

R	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Methyl	164	62	$C_{11}H_{12}N_2O_2S$	55.91	66.12	5.12	5.04
Ethyl	196	69	$C_{12}H_{14}N_2O_2S$	57.58	57.71	5.64	5.82
n-Propyl	142	90	$C_{13}H_{15}N_2O_2S$	59.06	59.13	6.10	6.33
i-Propyl	151.5	85	$C_{13}H_{16}N_2O_2S$	59.06	59.18	6.10	5.87
n-Butyl	116	76	$C_{14}H_{18}N_2O_2S$	60.40	60.22	6.52	6.35
i-Butyl	147	75	$C_{14}H_{18}N_2O_2S$	60.40	60.75	6.52	6.45
n-Amyl	107	63	$C_{15}H_{20}N_2O_2S$	61.61	61.83	6.90	6.88
n-Hexyl	114.5	70	$C_{16}H_{22}N_2O_2S$	62.71	62.71	7.24	7.12
Cyclohexyl	180	78	$C_{15}H_{20}N_2O_2S$	63.13	63.46	6.62	6.66
Phenyl	215	97	$C_{16}H_{14}N_2O_2S$	64.11	64.45	4.73	4.78
Benzyl	174	90	$C_{17}H_{16}N_2O_2S$	65.36	65.42	5.16	5.14

Bucherer.[6] The yields were good and recrystallization of the products removed the mercaptan odor. Yields and properties of the 5-R-thiomethyl-5-phenylhydantoins are summarized in Table II.

The 5-R-sulfonylmethyl-5-phenylhydantoins shown in Table III may be prepared by conversion of the corresponding oxidized α-R-thioacetophenones to the hydantoins; however, the 5-R-thiomethyl-5-phenylhydantoins are easily oxidized to the corresponding sulfonyl compounds.

TABLE III

5-R-SULFONYLMETHYL-5-PHENYLHYDANTOINS

R	M. p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	234	70	$C_{11}H_{12}N_2O_4S$	10.44	10.54
Ethyl	240	74	$C_{12}H_{14}N_2O_4S$	9.93	10.06
n-Propyl	219	80	$C_{13}H_{16}N_2O_4S$	9.46	9.34
i-Propyl	239	76	$C_{13}H_{16}N_2O_4S$	9.46	9.44
n-Butyl	195	84	$C_{14}H_{18}N_2O_4S$	9.03	8.92
i-Butyl	221.5	80	$C_{14}H_{18}N_2O_4S$	9.03	8.87
n-Amyl	175	72	$C_{15}H_{20}N_2O_4S$	8.64	8.47
n-Hexyl	177	70	$C_{16}H_{22}N_2O_4S$	8.28	8.00
Cyclohexyl	261	75	$C_{15}H_{20}N_2O_4S$	8.33	7.97
Phenyl	277	90	$C_{16}H_{14}N_2O_4S$	8.48	8.42
Benzyl	210	85	$C_{17}H_{16}N_2O_4S$	8.14	8.16

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

The oxidations were performed with hydrogen peroxide in acetic acid and acetic anhydride as in the method used by D'Ouville and Conner.[7]

Pharmacology.—The anticonvulsant activity of the substituted hydantoins herein described has been reported elsewhere in detail.[8] All of the compounds in Table II with the exception of 5-*n*-hexylthiomethyl- and 5-phenylthiomethyl-5-phenylhydantoin were found to be active. 5-*n*-Butylthiomethyl-5-phenylhydantoin was the most active compound, comparing favorably with Dilantin. Oxidation of the sulfur atom to the sulfonyl group usually resulted in a decrease in activity.

Experimental

α-Ethylthioacetophenone.—To a cooled solution of 20 g. of sodium hydroxide in 400 ml. of 50% alcohol was added slowly with frequent shaking 31.1 g. (0.5 mole) of ethyl mercaptan. To the resulting solution was added in one portion 77.3 g. (0.5 mole) of phenacyl chloride. The mixture was refluxed for forty-five minutes, cooled and diluted with two volumes of water. The mixture was extracted twice with 100-ml. portions of ether. The ether extracts were combined and dried over sodium sulfate. After filtration and removal of the ether, fractionation of the resi-

(7) D'Ouville and Conner, THIS JOURNAL, **60**, 33 (1938).

(8) Merritt, Putnam and Bywater, *J. Pharmacol.*, **84**, 67 (1945).

due yielded 79 g. (87%) of an almost colorless liquid, b. p. 106° (2 mm.); $n^{20}D$ 1.5700.

Anal. Calcd. for $C_{10}H_{12}OS$: C, 66.63; H, 6.71. Found: C, 66.83; H, 6.99.

The ketone was also prepared by an alternate procedure. Ninety grams (0.65 mole) of ethylthioglycolyl chloride, prepared in 90% yield from ethylthioglycolic acid[9] and thionyl chloride, was dissolved in 400 ml. of dry benzene. To the cooled solution was added with stirring 93.3 g. (0.7 mole) of anhydrous aluminum chloride in small portions. After the addition was complete (two hours) the mixture was stirred for two hours. About 300 ml. of cold dilute hydrochloric acid was added with stirring. The benzene layer was removed, dried and distilled. The product consisted of 75 g. (64%) of a pale yellow liquid, b. p. 104° (1.5 mm.); $n^{20}D$ 1.5700.

5-Ethylthiomethyl-5-phenylhydantoin.—The method of Bucherer was employed.[6] To a solution of 36 g. (0.2 mole) of α-ethylthioacetophenone in 600 ml. of 70% ethanol was added 18 g. of potassium cyanide and 56 g. of ammonium carbonate. The flask, fitted with a large bore air condenser, was heated on a water-bath at 55–60° for eight hours. The solution was evaporated to about 300 ml. on a steam-bath and then acidified with cold dilute hydrochloric acid. An oil precipitated which quickly solidified. The cooled mixture was filtered and the residue washed with cold water. The product was purified by dissolving in 5% sodium hydroxide solution, extracting three times with small portions of ether to remove unreacted ketone and reprecipitating with hydrochloric acid. After recrystallization from dilute ethanol the product weighed 34.5 g. (69%); m. p. 196°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64. Found: C, 57.71; H, 5.82.

5-Ethylsulfonylmethyl-5-phenylhydantoin.—To a mixture of 12.5 g. (0.05 mole) of 5-ethylthiomethyl-5-phenylhydantoin in 100 ml. of glacial acetic acid and 25 ml. of acetic anhydride was added 25 ml. of 30% hydrogen peroxide. A clear solution was formed after a few minutes when the heat of reaction had raised the temperature several degrees. When the temperature has increased to 70°, the flask was immersed in ice water for a short time in order to keep the temperature below 80°. After about one hour the solution was poured into two volumes of cold water. A white solid precipitated which was filtered off and recrystallized from alcohol. The yield of pure product was 9.3 g. (74%), m. p. 240°.

Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: N, 9.93. Found: N, 10.06.

(9) Ramberg, *Ber.*, **40**, 2588 (1907).

Summary

A number of α-R-thioacetophenones have been prepared and converted to the corresponding hydantoins which, in general, possess definite anticonvulsant activity.

Oxidation of 5-R-thiomethyl-5-phenylhydantoins to 5-R-sulfonylmethyl-5-phenylhydantoins usually resulted in decreased activity.

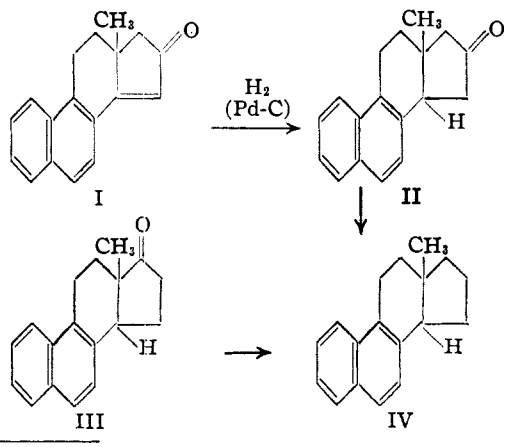
DETROIT, MICHIGAN RECEIVED JULY 18, 1946

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTY OF THE UNIVERSITY OF WISCONSIN]

cis and *trans dl*-Equilenane

BY A. L. WILDS, LLOYD W. BECK AND THOMAS L. JOHNSON

Recently[1] a method was described leading to the synthesis of the unsaturated ketone I having the carbon skeleton of the female sex hormone equilenin, but with the keto group in the 16- rather than the 17-position and lacking the 3-hydroxyl group.[2] By selective reduction using palladium on charcoal as the catalyst it was possible to hydrogenate I to 16-equilenone (II).[1]



Since only one of the two possible racemic mixtures corresponding to II could be isolated, it was of interest to determine its stereochemical configuration for rings C and D, relative to the isomeric 17-equilenones (III).

The synthesis of the *cis* and *trans* isomers of 17-equilenone has been described by Bachmann and Wilds,[3] using the general method employed for the synthesis of equilenin.[4] Each of the 17-equilenones has now been reduced to the corresponding *cis* and *trans* isomers of the parent hydrocarbon equilenane (IV),[5] and these have been compared with the hydrocarbon obtained by reduction of the 16-equilenone isomer. Clemmensen reduction of 16-equilenone gave a solid which was purified through the picrate and by repeated recrystallization to the equilenane (IV) having a melting point of 87.5–89.5°. Wolff–Kishner reduction of the semicarbazone was less satisfactory. The hydrocarbon formed a crystalline picrate and *s*-trinitrobenzene complex.

Clemmensen reduction of α-17-equilenone gave a liquid hydrocarbon which could not be crystallized, but could be converted into crystalline

(1) Wilds and Beck, THIS JOURNAL, **66**, 1688 (1944).

(2) The successful extension of this method to the related compounds having the 3-hydroxyl group (by Warren J. Close) and also with ring B hydroaromatic (by Thomas L. Johnson) will be reported shortly.

(3) Bachmann and Wilds, *ibid.*, **62**, 2084 (1940); this paper may also be referred to for the nomenclature of these compounds.

(4) Bachmann, Cole and Wilds, *ibid.*, **62**, 824 (1940).

(5) The first reduction experiments on the 17-equilenones were carried out by one of us (A. L. W.) in Dr. Bachmann's laboratory in 1939.