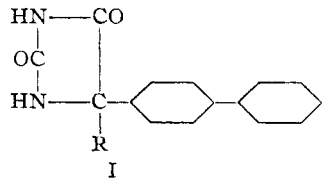
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

5-(4-Biphenylyl)-5-R-hydantoins and Bis-5-[(4-phenyl)-5-R-hydantoin]s[1]

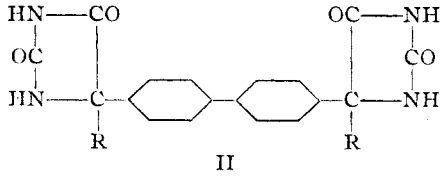
BY HENRY R. HENZE AND LOREN M. LONG[2]

As hypnotic medicinals, the 5,5-disubstituted hydantoins have proved disappointing; but in the control of certain types of epilepsy, one derivative, namely, 5,5-diphenylhydantoin (Dilantin), is proving more satisfactory than either 5-ethyl-5-phenylhydantoin (Nirvanol) or 5-ethyl-5-phenylbarbituric acid (Phenobarbital). It will be noted that a phenyl substituent is common to all three of these drugs. The hypnotic effect is least and the anticonvulsant activity greatest in the diphenyl compound.

In view of these facts, it seemed of interest to us to prepare new hydantoins bearing some resemblance to Nirvanol and Dilantin, yet distinctly different from any which previously we had prepared for pharmacological testing. It was felt that the synthesis of biphenyl-hydantoins would accomplish this object. Especially desirable should be the production of hydantoins of types I and II in which R represents either the ethyl or phenyl group.



I



II

The usual method for conversion of a ketone into a 5,5-disubstituted hydantoin is that of Bucherer,[3] but diaryl ketones react not at all or only with extreme slowness in this procedure. For example, 4-biphenylyl phenyl ketone gave a yield of only 1.2% of the related hydantoin when warmed at 57° for seventy-two hours under the usual conditions developed by Bucherer. Likewise, 4-biphenylyl methyl ketone required fifty hours to produce a 67% yield of hydantoin, while bis-(4-phenyl methyl ketone) after forty-five hours yielded 56% of the desired bis-hydantoin. These data are to be contrasted with the higher yields listed in Tables I and II obtained in but one-fifth to one-fourth of these periods of heating using a different solvent and temperature for reaction.

We have modified Bucherer's process in an essential manner through use of fused acetamide[4] as the solvent, and, by means of such modification, have prepared a total of twenty-one new hydantoins. With reference to the structures formulated as Types I and II, R- includes the methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *n*-amyl, isoamyl, *n*-hexyl and phenyl[5] groups. In addition, we have prepared two compounds of Type I in which R- is the 1-methylbutyl or 1-ethylpropyl grouping.

The bis-5-[(4-phenyl)-5-R-hydantoin]s reported in this investigation represent the results of the first wholly successful attempt to synthesize this type of compound. Where the two carbonyls of a diketone are adjacent, usually such diketone cleaves, when exposed to the influence of potassium and ammonium carbonate solution, and yields a 5-monosubstituted hydantoin.

Through the courtesy of Parke, Davis and Company, to whom our thanks are due for their financial aid and assistance, most of these biphenylhydantoins have received preliminary pharmacological testing. As yet, no evidence of hypnotic or anticonvulsant activity has been detected, but analgesic action is evidenced by the butyl-, amyl- and hexyl-hydantoins.

Experimental

Preparation of 5-Alkyl(or Phenyl)-5-(4-biphenylyl)-hydantoins.—In preparing these compounds 125–150 g. of acetamide was placed in the Pyrex glass liner of a Monel metal bomb and warmed until the acetamide had fused. Then 0.05 mole of a biphenyl ketone,[6] C_6H_5–C_6H_4–CO–R, was dissolved in the amide and 4.5 g. of potassium cyanide was added with stirring until the cyanide had gone into solution. [This precaution is necessary, since otherwise a

(1) Presented before the Division of Medicinal Chemistry at the 101st meeting of the American Chemical Society at St. Louis, Missouri, April 10, 1941.

(2) Parke, Davis and Company Research Fellow.

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

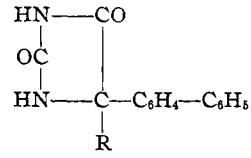
(4) Henze and Long, THIS JOURNAL, **63**, 1936 (1941).

(5) 5-(4-Biphenyl)-5-phenylhydantoin was first prepared by Hatt, Pilgrim and Hurran (*J. Chem. Soc.*, 93 (1936)) from interaction of 4-phenylbenzil with urea and potassium hydroxide. The diketone was obtained through oxidation of diphenyl benzyl ketone by selenium dioxide.

(6) Long and Henze, THIS JOURNAL, **63**, 1939 (1941).

TABLE I

5-(4-BIPHENYLYL)-5-R-HYDANTOINS

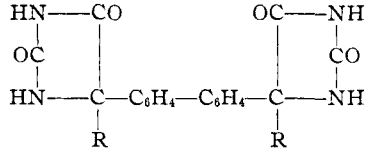


R	M. p., °C. (cor.)	Yield, %	Nitrogen, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
$-CH_3$	295.0	90	10.52	10.61	72.16	72.28	5.30	5.28
$-C_2H_5$	256.0	85	10.00	9.99	72.84	72.73	5.75	5.73
$-CH_2CH_2CH_3$	201.5–202.5	88	9.52	9.52	73.45	73.60	6.16	6.14
$-CH(CH_3)_2$	270.0–271.0	87	9.52	9.58	73.45	73.25	6.16	6.17
$-CH_2CH_2CH_2CH_3$	199.5	90	9.09	9.00	74.00	73.88	6.54	6.63
$-CH_2CH(CH_3)_2$	224.0–225.0	78	9.09	9.14	74.00	73.93	6.54	6.56
$-CH_2CH_2CH_2CH_2CH_3$	195.0–196.5	83	8.69	8.83	74.50	74.34	6.88	6.95
$-CH_2CH_2CH(CH_3)_2$	232.0–233.0	88	8.69	8.60	74.50	74.44	6.88	6.82
$-CH(CH_3)C_3H_7$	262.0	71	8.69	8.78	74.50	74.59	6.88	6.89
$-CH(C_2H_5)_2$	249.0–250.0	73	8.69	8.79	74.50	74.25	6.88	6.98
$-CH_2CH_2CH_2CH_2CH_2CH_3$	185.0–186.5	80	8.33	8.41	74.97	74.84	7.19	7.20
$-C_6H_5$[a]	242.0	74	8.53	8.67	76.82	76.65	4.91	4.96

[a] See ref. 5.

TABLE II

BIS-5-[(4-PHENYL)-5-R-HYDANTOIN]S



R	M. p., °C. (cor.)	Yield, %	Nitrogen, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
$-CH_3$	360	56	14.81	14.92	63.48	63.53	4.79	4.80
$-CH_2CH_3$	335	80	13.79	13.61	65.01	64.78	5.46	5.41
$-CH_2CH_2CH_3$	214	75	12.90	12.92	66.34	66.51	6.03	6.08
$-CH(CH_3)_2$	360	80	12.90	13.01	66.34	66.24	6.03	6.12
$-CH_2CH_2CH_2CH_3$	310	79	12.11	12.02	67.51	67.20	6.54	6.65
$-CH_2CH(CH_3)_2$	295	76	12.11	12.23	67.51	67.33	6.54	6.59
$-CH_2CH_2CH_2CH_2CH_3$	312	65	11.42	11.30	68.55	68.54	6.99	7.07
$-CH_2CH_2CH(CH_3)_2$	335	71	11.42	11.35	68.55	68.52	6.99	7.02
$-CH_2CH_2CH_2CH_2CH_2CH_3$	284	70	10.80	10.93	69.47	69.63	7.39	7.40
$-C_6H_5$	282	53	11.15	10.91	71.70	72.00	4.41	4.30

dark layer of decomposed material forms on the bottom of the container during the course of the reaction and colors the product.] The liner was placed in the bomb, 14.4 g. of ammonium carbonate cubes was added, and the bomb was closed at once to avoid loss of ammonia and carbon dioxide. The bomb was then placed in an oven regulated at 110° and heated for eight hours.

On cooling the bomb to room temperature and opening, the semi-solid product was mixed with 500 cc. of water in a large beaker and acidified (Hood!) with hydrochloric acid. After the foaming had subsided, the solid material was filtered and treated with 300–400 cc. of 5% sodium hydroxide solution and filtered to remove unchanged ketone (if any). The filtrate was acidified with hydrochloric acid and the precipitate (light yellow to dark tan in color) was filtered, dried and recrystallized until colorless. For purification, solution in acetone with subsequent addition of water was most generally satisfactory; however, in most cases recrystallization was employed from a second solvent such as dioxane, ethyl alcohol or acetic acid. Data for the twelve new hydantoins synthesized in this manner are collected in Table I.

Preparation of the bis-5-[(4-Phenyl)-5-alkyl(or phenyl)-hydantoin]s.—The preparation of the bis-[(4-phenyl)-R-hydantoin]s differed but little from that of the 5-(4-biphenylyl)-5-R-hydantoins. For 0.05 mole of a bis-phenyl ketone,[6] 9 g. of potassium cyanide and 28.8 g. of ammonium carbonate cubes were used and the reaction mixture was heated in the bomb at 110° for twelve hours. The bis-hydantoins dissolve in 5% sodium hydroxide more slowly than do the monohydantoins and are likewise reprecipitated more slowly on acidification. These compounds tend to assume a grainy appearance on crystallizing, but are seen to be very small, needle-like crystals under the microscope. Only one compound, bis-5-(4-phenyl-5-*n*-propylhydantoin), persisted in precipitating as a liquid and then slowly solidifying. The melting point of this hydantoin appears to be considerably lower than would

be expected on the basis of the melting points of the other members of the series. Certain data concerning these ten new hydantoins are listed in Table II.

Summary

Using fused acetamide as a solvent, our modification of the Bucherer process has been employed in the synthesis of twenty-one new hydantoins. Eleven of these contain a biphenyl grouping attached to the hydantoin nucleus; ten are of the bis-hydantoin type in which two hydantoin nuclei are joined through the biphenyl group.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of 5-Disubstituted Aminomethyl-5-phenethylhydantoins[1]

BY HENRY R. HENZE AND CHARLES B. HOLDER[2]

The preparation of a series of 5-disubstituted aminomethyl-5-methylhydantoins from disubstituted aminoacetones, $CH_3COCH_2NR_2$, has been reported recently.[3] However, there is ample reason to anticipate that derivatives of dimethylhydantoin would have less physiological activity than those disubstituted hydantoins in which each substituent is a higher alkyl or a phenyl group. Likewise certain unpublished work in this Laboratory has indicated that the phenethyl group has but little hypnotic activity but considerable anticonvulsant value. Therefore the present investigation involved the preparation of related hydantoins in which one substituent should be the phenethyl group. Synthesis of the desired hydantoins from appropriate phenethyl ketones could be anticipated by utilization of Bucherer's[4] method.

Production of seven disubstituted aminomethyl phenethyl ketones, $R_2NCH_2COCH_2CH_2C_6H_5$, was effected by interaction of appropriate secondary amines and 1-chloro-4-phenylbutanone-2[5] following the procedure developed in this Laboratory.[3] Although this chloro ketone[5] had been prepared from diazomethane and hydrocinnamoyl chloride, we preferred to attempt its synthesis by oxidation of the corresponding secondary alcohol, namely, 1-chloro-4-phenylbutanol-2, which was available through interaction of epichlorohydrin and benzylmagnesium chloride.[6,7] Although the yield realized from the Grignard reaction is less than that reported using diazomethane, utilization of a poisonous and explosive substance was avoided.

1-Chloro-4-phenylbutanone-2 was utilized in the preparation of the six new disubstituted aminomethyl phenethyl ketones listed in Table I. By interaction of each of these amino ketones with potassium cyanide and ammonium carbonate, the corresponding 5-disubstituted aminomethyl-5-phenethylhydantoins were obtained. This represents the initial synthesis of these six compounds, as well as of 5-(N-ethyl-N-phenylaminomethyl)-5-phenethylhydantoin, the latter being prepared from an only partially purified sample of the corresponding ketone. Certain data for these seven hydantoins are listed in Table II.

Experimental

1-Chloro-4-phenylbutanol-2.—The preparation of this compound was accomplished through the method described by Koelsch and McElvain.[7] The chlorohydrin was obtained initially as a liquid; b. p. 112–114° (4 mm.), $n^{20}D$ 1.5378, d^{20}_4 1.1282, M_R calcd. 51.17, M_R found 51.18. However, the product solidified; yield 45% of the theoretical; after three recrystallizations from petroleum ether, m. p. 46–47° (cor.).

Anal. Calcd. for $C_{10}H_{13}ClO$: C, 65.04; H, 7.10; Cl, 19.20. Found: C, 64.90; H, 7.10; Cl, 19.15.

1-Chloro-4-phenylbutanone-2.—This chloro ketone was prepared by the chromic acid oxidation[8] of 1-chloro-4-phenylbutanol-2. From 194.5 g. of the latter, there was obtained 157.5 g. (82% yield) of solid melting at 35–40°; after recrystallization from alcohol–water and from petroleum ether, m. p. 40–41° (cor.). The melting point was lowered only about 1.5° by fusion, continued heating to 120°, solidification and refusion.

Since Clibbens and Nierenstein[5] had reported a melting point of 84–85° for this compound, the apparently pure chloro ketone was distilled under diminished pressure and

(1) Presented before the Division of Organic Chemistry at the 101st meeting of the American Chemical Society at St. Louis, Missouri, April 8–10, 1941.

(2) From the Ph.D. dissertation of C. B. Holder, June, 1941.

(3) Magee and Henze, THIS JOURNAL, **60**, 2148 (1938).

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

(5) Clibbens and Nierenstein, *J. Chem. Soc.*, **107**, 1493 (1915).

(6) Fourneau and Tiffeneau, *Bull. soc. chim.*, [4] **1**, 1231 (1907).

(7) Koelsch and McElvain, THIS JOURNAL, **52**, 1164 (1930).

(8) We adopted the directions for the preparation of *sym*-dichloroacetone ["Organic Syntheses," John Wiley and Sons, Inc., New York, Collective Volume I, 1932, page 206] except that 50% acetone–water solution served as solvent.