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

SYNTHESIS OF 5-BENZOHYDRYL-5-SUBSTITUTED HYDANTOINS[1]

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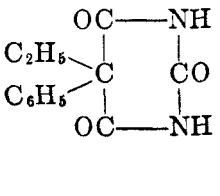
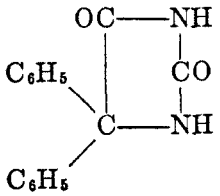
Received April 3, 1950

At present, there is no cure for epilepsy based upon the administration of medicinals. However, a satisfactory though temporary relief is noted in many epileptic individuals during the period of their continued use of phenobarbital[3] (I), Dilantin[4] (II), or Mesantoin[5] (III), or a combination of the former with one of



I



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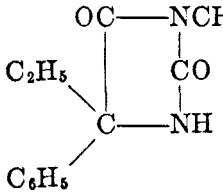


III

the hydantoin derivatives. Phenobarbital, perhaps, is superior to Dilantin in the alleviation of the *petit mal* type of epilepsy (1), but is likely to produce central depression and hypnosis in the dosages required to control the *grand mal* type. Dilantin is most widely employed in treatment of the *grand mal* and psychomotor seizures and does not usually exhibit hypnotic effect. Although Dilantin appears to possess the greater margin of safety with regard to fatal dose, it frequently produces toxic reactions to a mild degree when administered to epileptics. The formula of Mesantoin (III) reveals that it is a 3-methyl derivative of nirvanol, 5-ethyl-5-phenylhydantoin (2), use of which was discontinued because of its production of a characteristic and very disagreeable skin eruption.[6]

It was at one time concluded that the anti-epileptic activity of certain barbiturates, hydantoins, and aryl ketones may be due to the presence of phenyl groups in their structures (3). While it is true that essentially all of the hydantoin derivatives of pronounced anticonvulsant activity do possess at least one phenyl

[1] From the Ph.D. dissertation of William B. Leslie, June, 1944.

[2] Present address: Clovis, New Mexico.

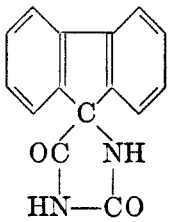
[3] Phenobarbital, U.S.P., 5-ethyl-5-phenylbarbituric acid, used also in the form of its sodium salt.

[4] Dilantin, trade mark of Parke, Davis and Company for the sodium salt of 5,5-diphenylhydantoin, Diphenylhydantoin, U.S.P.

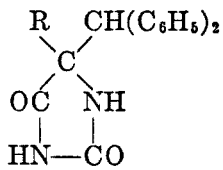
[5] Mesantoin, trade mark of Sandoz Chemical Company for 5-ethyl-3-methyl-5-phenylhydantoin.

[6] It is of considerable interest that Sabotka, Holzman, and Kahn, *J. Am. Chem. Soc.*, **54**, 4697 (1932); *Am. J. Diseases Children*, **45**, 1216 (1933) have been able to accomplish the resolution of this racemic hydantoin; apparently, the *dextro*-isomer is essentially free from this undesirable effect upon the skin.

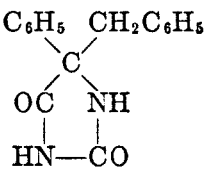
group attached directly to the 5-C position of the heterocyclic nucleus (4, 5), the requirement of this partial structure for such activity has not been demonstrated. A few hydantoins, such as the 5,5-dithienyl derivative, and some other compounds, such as Tridione,[7] which are not hydantoins, are powerful anticonvulsants, while a large number of 5-phenyl-5-substituted hydantoins are without any measurable degree of this activity (5). In short, no absolute relationship between structure and anticonvulsant activity has, as yet, been established. For the time being, while awaiting the development of a more rational approach, search for better anticonvulsants is likely to continue to involve synthesis of heterocyclic compounds having one or more phenyl substituents.



IV



V



VI

A *spiro*-hydantoin (IV), 5,5-biphenylenehydantoin, first synthesized in this laboratory (6), has been found to possess considerable anticonvulsant activity; enough, indeed, to warrant some clinical testing. The close structural similarity of IV to II is obvious. As far as is known, there have been no substituted hydantoins which possess two phenyl groups attached indirectly to the 5-C position of hydantoin, that is, as the benzohydryl grouping, subjected to pharmacological investigation. It should be noted that 5-benzohydrylhydantoin (V, R = H) is isomeric with 5-benzyl-5-phenylhydantoin (VI) which is known to be strongly anticonvulsant. Therefore, synthesis of a few examples of this type (V) was the purpose of this investigation.

The sequence selection for preparation of such 5-benzohydrylhydantoins (V) was as follows:

$$RCHO \rightarrow RCHOHCN \rightarrow RCHOHCOOC_2H_5 \rightarrow RCH(OMgBr)C(OMgBr)(C_6H_5)_2 \rightarrow RCHOHC(OH)(C_6H_5)_2 \rightarrow RCOCH(C_6H_5)_2 \rightarrow V$$

There are available several patents describing processes whereby esters of α-hydroxy acids may be prepared from cyanohydrins. One of these processes (7) was selected because it allows the preparation of the ester directly from the aldehyde, without isolation of the intermediate cyanohydrin.

The hydroxy esters were used for the preparation of 1,1-diphenyl-1,2-glycols. The ketones necessary for production of the hydantoins were obtained through dehydration of the glycols by means of 25% sulfuric acid. The synthesis of the hydantoins was accomplished by the method of Henze and Long (8). Through the courtesy of Parke, Davis and Company, these five hydantoin derivatives

[7] Tridione (Trimethadione, N.N.R.) is the trade mark of Abbott Laboratories for 3,5,5-trimethyloxazolidine-2,4-dione which is particularly valuable in control of *petit mal*.

have received pharmacological testing. The three 5-alkyl-5-benzohydrylhydantoins possess considerable anticonvulsant activity but are quite toxic, the methyl derivative tending to produce convulsions. 5-Benzohydrylhydantoin and 5-benzohydryl-5-phenylhydantoin are without anticonvulsant activity in the dosages employed. Thus, again, it is demonstrated that the mere presence of the 5-phenyl substituent does not insure anticonvulsant activity of the hydantoin,

TABLE I

ETHYL ESTERS OF CERTAIN α-HYDROXY ACIDS, $RCHOHCOOC_2H_5$

R—	B.P., °C.	MM.	YIELD, %	d_4^{20}	n_D^{20}	MOLECULAR REFRACTION	
						Σ	Calc'd
H[a]	69 157.7–157.9	25 754	55.0	1.1005	1.4180	23.85	23.84
CH_3[b]	65.5 153.0–153.2	25 754	45.0	1.0341	1.4131	28.47	28.49
C_2H_5[c]	74.5 167.0	25 747	57.0	1.0069	1.4179	33.09	33.08
C_3H_7[d]	88.5 184.3–184.6	25 745	57.5	0.9839	1.4220	37.75	37.71
C_6H_5[e]	127 264.5–265.5	9 756	52.5	1.1258[f]	1.5136[f]	47.96	48.16

[a] Schreiner, *Ann.*, **197**, 1 (1897), reported b.p. 160° (cor.) (760 mm.); d^{23} 1.0826; Palomaa, *Ann. Acad. Sci. Fennicae*, **A4**, 1 (1913); through *Chem. Zentr.*, **84**, II, 1959 (1913), reported b.p. 158°; d_4^{15} 1.0869. [b] Schreiner, *Ann.*, **197**, 1 (1897), reported b.p. 154.5° (cor.) (760 mm.); d_{25}^{19} 1.0308; Smith and Claborn, *Ind. Eng. Chem.*, **32**, 692 (1940), reported $n^{25}D$ 1.4121; Walden and Swinne, *Z. physik. Chem.*, **79**, 723 (1912), recorded d_4^{25} 1.0299. [c] Schreiner; *Ann.*, **197**, 1 (1897), reported b.p. 167° (cor.) (760 mm.); d^{10} 0.9952. [d] Menozzi, *Gazz. chim. ital.*, **14**, 19 (1884), reported b.p. 190°; d^{15} 0.9883. Nicolle, *Bull. soc. chim.*, **2** 150, (1938), reported b.p. 170–180° (760 mm.). [e] Beyer, *J. prakt. Chem.*, [2] **31**, 389 (1885), reported b.p. 253–255°; Darapsky, *J. prakt. chem.*, (2) **96**, 297 (1917), reported b.p. 141° (15 mm.); McKenzie, *J. Chem. Soc.*, **75**, 755 (1899), reported m.p. 37°; Michael and Jeanpretre, *Ber.*, **25** 1784 (1892), claimed m.p. 34°; Findlay and Turner, *J. Chem. Soc.*, **87**, 753 (1905), reported "the ester obtained in this work melted at 29° after fractionation and at 30° after recrystallization . . . but could not be raised by further recrystallizations." [f] These data were obtained on supercooled liquid material; the product solidified, m.p. 30°.

nor does the absence of the 5-phenyl substituent preclude anticonvulsant activity in this series.

EXPERIMENTAL

Preparation of the ethyl esters of α-hydroxy acids. In general, 200 ml. of dioxane, 2.74 moles of a carefully-fractionated aldehyde, and 0.4–0.5 g. of sodium hydroxide dissolved in 39.3 g. (2.18 moles) of water were placed in a flask provided with a thermometer, mechanical stirrer, and dropping-funnel the stem of which extended well into the lower portion of the flask. Meanwhile, 77 g. (2.74 moles) of commercial grade (96%) liquid hydrogen cyanide was

drawn into a 250-ml. flask and diluted with 50 ml. of cold dioxane.[8] The reaction flask was immersed in an ice-bath and the hydrogen cyanide-dioxane mixture was added slowly through the dropping-funnel into the well-stirred, alkaline solution of the aldehyde.[9] The reaction was exothermic but was maintained below 25°. If evolution of heat ceased, addition of a few drops of concentrated sodium hydroxide solution hastened the reaction. The stirred reaction mixture was allowed to come to room temperature and then was heated to about 75°.

After the mixture had cooled to room temperature, the flask was placed in an ice-salt mixture, and 199 g. (4.11 moles) of 95% ethyl alcohol (containing 0.55 mole of water) was added, and the dropping-funnel was replaced by a glass inlet tube, through which a fairly

TABLE II

1,1-DIPHENYL-1,2-DIOLS, $(C_6H_5)_2C(OH)CH(OH)R$

R	YIELD, %	M.P., °C. (cor.)
H[a]	58.5	122.5–123.0
CH_3[b, c, d]	78.5	95.2–95.4
C_2H_5[e, f, g]	92.0	92
C_3H_7[h]	89.0	89
C_6H_5[i]	72.5	166.5

[a] Tiffeneau, *Ann. chim.*, [8] **10**, 344 (1907) reported m.p. 122°; Pall and Weidenkaff, *Ber.*, **39**, 2063 (1906), prepared this glycol (m.p. 121°) from ethyl glycolate in 44% yield. [b] When this preparation was repeated employing 183 g. (1.16 moles) of bromobenzene, 30.5 g. (1.26 gram-atoms) of magnesium and 600 ml. of absolute ether to prepare the Grignard reagent [by this method a 94.7% yield of the Grignard reagent has been obtained, see *J. Am. Chem. Soc.*, **51**, 1576 (1929)] an 82.3% yield of the glycol was obtained starting from 39.4 g. (0.33 mole) of ethyl lactate. [c] Stoermer and Riebel, *Ber.*, **39**, 2302 (1906), prepared this glycol by the interaction of 30 g. (0.125 mole) of ethyl lactate with phenylmagnesium bromide prepared from 79.8 g. (0.51 mole) of bromobenzene and 12.3 g. (0.51 gram-atom) of magnesium. Since each mole of ester requires three moles of Grignard reagent, it is evident that this reaction was carried out with a deficiency of phenylmagnesium bromide. The melting point of the recrystallized product was reported as 96.5°. [d] Smith and Hoehn, *J. Am. Chem. Soc.*, **63**, 1177 (1941), prepared this glycol in but 38% yield (calculated on the basis of the ester used) because they repeated the error made by Stoermer and Riebel; m.p. 95°. [e] Roger, *Helv. Chim. Acta*, **12**, 1061 (1929), prepared this glycol from ethyl α-hydroxybutyrate and phenylmagnesium bromide, in 55% yield; m.p. 115–116°. [f] McKenzie and Roger, *J. Chem. Soc.*, 571, (1927) prepared this glycol by a molecular arrangement of 2,3-diphenyl-2-hydroxybutylamine. [g] *Anal.* Calc'd for $C_{16}H_{16}O_2$: C, 79.31; H, 7.49. Found: C, 79.45; H, 7.64. [h] *Anal.* Calc'd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 79.56; H, 8.04. [i] Acree, *Ber.*, **37**, 2863 (1904), reported m.p. 167°.

rapid stream of dry hydrogen chloride was passed. The temperature of the reaction mixture was kept below 20° until saturation was complete (about two hours), then the flask was fitted with a condenser and heated for a period of 5½ hours at the reflux temperature; considerable ammonium chloride separated. After cooling, the salt was removed by filtration,

[8] Since hydrogen cyanide boils at 26°, its vapor pressure at room temperature is decreased appreciably by dilution with dioxane.

[9] The reaction proceeded equally well if the aldehyde was added through the dropping-funnel to the hydrogen cyanide dissolved in the dioxane and sodium hydroxide solution. This sequence of addition might be advantageous in case the aldehyde readily undergoes the aldol type of condensation.

the filter cake was washed with 50 ml. of dioxane, and the washings were added to the filtrate which was replaced in the flask and saturated with ammonia at ice-bath temperature. Again, precipitated ammonium chloride was filtered off and washed with dioxane. The filtrate was distilled at 150 mm. using a warm-water bath as source of heat. The ester was distilled at 25 mm. or less; considerable still residue resulted. The ester was redistilled

TABLE III

BENZOHYDRYL KETONES, $(C_6H_5)_2CHCOR$

R	M.P., °C. (cor.)	B.P., °C.	MM.	YIELD, %	n_D^{20}	d_4^{20}	MOLECULAR REFRACTION	
							Σ	Calc'd
H[a]		116–117	1.5	49	1.5893	1.0980	59.66	60.26
CH_3[b]	60.0–60.5			92				
C_2H_5[c, d]	29	130–131	1.5	93				
C_3H_7[e, f]				95	1.5621	1.0436	73.52	74.06
C_6H_5[g, h]	138.0–138.5			43				

[a] Behal and Sommelet, *Bull. soc. chim.*, [3] **31**, 307 (1904), prepared a small quantity of diphenylacetaldehyde by dehydration of the glycol with oxalic acid and reported b.p. 168–170° (10 mm.); n_D^{19} 1.5899; d^{19} 1.1048; ΣMR 60.15; MR calc'd, 59.90. Klages and Kessler, *Ber.*, **39**, 1755 (1906), prepared this aldehyde by dehydration of the glycol by sulfuric acid and reported b.p. 166° (9 mm.); n_D^{21} 1.5920; d_4^{21} 1.1061; ΣMR 60.15; MR calc'd, 59.96. [b] Stoermer and Riebel, *Ber.*, **39**, 2302 (1906), prepared this ketone by heating the glycol with very dilute hydrochloric acid at 180°. The ketone was said to be dimorphic, for two forms were isolated; m.p. 46° and 61°. [c] Maxim, *Ann. chim.*, [10] **9**, 81 (1928), prepared this ketone in 31% yield by the interaction of diphenylacetamide and ethylmagnesium bromide; b.p. 186° (14 mm.); Roger, *Helv. Chim. Acta*, **12**, 1061 (1929), obtained a small amount of this ketone from dehydration of the glycol and reported b.p. 178° (17 mm.). [d] *Anal.* Calc'd for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.41; H, 7.33. [e] Billard, *Bull. soc. chim.*, [4] **29**, 429 (1921), reported the preparation of an impure sample of this ketone, of b.p. 185–192° (13 mm.), by the dehydration and rearrangement of 1,2-diphenyl-1-propyl-1,2-ethanediol. [f] *Anal.* Calc'd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.41; H, 7.59. [g] This ketone was prepared from 40 g. (0.14 mole) of 1,1,2-triphenylethane-1,2-diol and 150 ml. of 25% sulfuric acid. Because of the high melting point (166.5°) of the glycol, it was necessary to reflux the mixture vigorously for more than an hour. After filtration, the crude ketone stood overnight in contact with ether; after being dried, wt. 19.8 g.; m.p. 134–135°. Recrystallization from 500 ml. of Skellysolve C yielded 16.3 g. (43%) of white needles melting at 138.0–138.5°. The ether extract yielded 14.9 g. of product (m.p. 91–95°) which could not be brought to sharper m.p. than 90–100° after recrystallizations from several different solvents. In another preparation, 80 g. of trichloroacetyl chloride was allowed to react with 800 ml. of dry benzene in the presence of anhydrous aluminum chloride. Purification followed directions of Biltz, *Ber.*, **32**, 654 (1899), (who failed to report a m.p. for his product). After repeated recrystallizations from Skellysolve C, alcohol, glacial acetic acid, etc., a yellow crystalline powder (m.p. 135°) resulted. [h] Boyle, McKenzie, and Mitchel, *Ber.*, **70**, 2153 (1937), prepared this ketone from phenylmagnesium bromide and α-chlorophenylacetyl chloride, m.p. 135.5–136.5°.

through an efficient 25-cm., glass helices-packed column yielding products of about one or two degree boiling range. Table I lists the esters resynthesized.

Preparation of 1,1-diphenyl-1,2-glycols. A Grignard reagent was prepared from 27 g. (1.11 gram-atoms) of magnesium and 181 g. (1.15 moles) of bromobenzene in 450 ml. of anhydrous ether. The ethyl ester of the appropriate α-hydroxy acid (0.33 mole) was added to the reagent causing vigorous reaction. The mixture was heated for 2–3 hours while approxi-

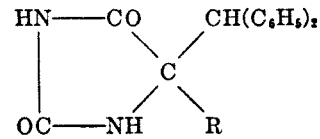
mately one-half of the solvent was distilled off. The resultant mixture was poured into 80 ml. of glacial acetic acid and 400 g. of cracked ice, and was stirred to dissolve any glycol present. After separation of the two layers, the ether layer was washed with dilute alkali and then with water before being warmed until the temperature reached 65°. After cooling to room temperature, the glycol was precipitated by the addition of two 50-ml. portions of Skellysolve F. One recrystallization was sufficient to yield the glycols listed in Table II.

Preparation of diphenylacetaldehyde and benzohydryl ketones. Approximately 0.2 mole of purified glycol and 100–150 ml. of 25% (by volume) sulfuric acid were heated to reflux temperature for about 3½ hours. The organic material was separated, and if solid was purified by crystallization from Skellysolve C or ethyl alcohol. The liquid ketones were purified by distillation at 1.5 mm. Data for these ketones are collected in Table III.

Preparation of 5-benzohydryl-5-substituted hydantoins. One-tenth mole of purified ketone was dissolved in 225 g. of molten, commercial grade acetamide, and 7.16 g. (0.11 mole) of potassium cyanide was added with stirring; the mixture was allowed to cool before 34 g. of ammonium carbonate was added. The reaction mixture was placed in a glass liner, sealed in a Monel pressure vessel and heated at 110° for 16 hours. After cooling, the mixture was dissolved in about 450 ml. of hot water, and was cooled and filtered. Acidification of the filtrate caused precipitation of solid material which was separated and combined with that obtained

TABLE IV

5-BENZOHYDRYL-5-SUBSTITUTED HYDANTOINS



R	YIELD, %	M.P., °C. (cor.)	N	
			Calc'd	Found
H	44	223.0–223.5	10.52	10.66
CH_3	76	265.0–265.5	10.00	9.95
C_2H_5	77	219.2–219.5	9.52	9.63
C_3H_7	68	236.7–236.9	9.06	8.84
C_6H_5	76	264.0–264.5	8.18	8.06

prior to acidification. The crude hydantoin was purified, either by solution in 10% sodium hydroxide solution, followed by filtration and reacidification, or by recrystallization from glacial acetic acid. In general, the benzohydrylhydantoins were quite soluble in hot glacial acetic acid, only moderately soluble in hot alcohol, and insoluble in water. For comparison with this procedure, which is that developed by Henze and Long (8), the procedure of Bucherer and Lieb (9) was tried for preparation of the methyl and propyl analogs. This method gave a slightly larger yield of crude methyl derivative, but a much poorer yield of the propyl product. Data for these benzohydrylhydantoins are collected in Table IV.

In the case of benzohydryl phenyl ketone, owing to its low solubility, it was necessary to employ 440 g. of molten acetamide for the 0.1 mole of ketone. The crude hydantoin, after trituration with hot benzene melted at 264.0–264.5°; recrystallization from glacial acetic acid or diluted alcohol failed to alter the melting point.

Anal. Calc'd for $C_{22}H_{18}N_2O_2$: N, 8.18. Found: N, 7.16.

A 0.4347-g. sample of this material was heated for two hours at 150° and 10 mm. pressure and was found to have lost 0.0434 g.; the melting point remained 264.0-264.5°.

Anal. Calc'd for $C_{22}H_{18}N_2O_2$: N, 8.18. Found: N, 8.08.

From the mother liquor in this preparation there was recovered 10.5 g. of unreacted ketone.

SUMMARY

Five 1,1-diphenyl-1,2-glycols, one of which was new, have been prepared from ethyl esters of α-hydroxy acids by means of the Grignard reaction.

The glycols were dehydrated to yield diphenylacetaldehyde and four benzohydryl alkyl or phenyl ketones.

These benzohydryl ketones have been converted into five, new 5-benzohydryl-5-substituted hydantoins.

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(4) MERRITT, PUTNAM, AND BYWATER, *J. Pharmacol. Exptl. Therap.*, **84**, 67 (1945).
(5) MERRITT AND PUTNAM, *Epilepsia*, **9**, 51 (1945).
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(7) German Patent 562,390; *Friedl.*, **19**, 417 (1934).
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