with sodium bicarbonate solution and dried. Distillation of the neutral oil in small quantities through a short column gave 600 g. (65% yield) of water-white (N-carballyldioxyethyl) allyl carbamate, b.p. 151–152° at 3 mm., d^{28}_4 1.142, $n^{28}D$ 1.4630.

Anal. Calcd. for $C_{10}H_{15}O_5N$: N, 6.11. Found: N, 5.83.

Bis-(N,N'-carballyloxy)-urea.—Phosgene was passed into 202 g. (2 moles) of allyl carbamate at 50–75° during a four-hour period. The solid product was filtered off and dissolved in hot ethyl alcohol. Crystallization from alcohol gave 125 g. (55% yield) of bis-(N,N'-carballyloxy)-urea, m.p. 70°.

Anal. Calcd. for $C_9H_{12}O_5N_2$: N, 12.30. Found: N, 11.80.

AKRON, OHIO

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

Hydantoins from Alicyclic Ketones and Aldehydes

BY EDWARD S. ROTHMAN AND ALLAN R. DAY

RECEIVED JUNE 26, 1953

A series of new hydantoins of the 1-, 5- and spiro-5,5-substituted types derived from alicyclic ketones and aldehydes have been synthesized. A stereoisomer of the spirohydantoin derived from *l*-menthone has been prepared and evidence is presented to demonstrate the optical purity of the isomer obtained from *l*-menthone. 1-*l*-Menthyl-5,5-diethylbarbituric acid and 1-*d*-bornyl-5,5-diethylbarbituric acid were prepared also.

It has been found recently that both the spirohydantoin prepared from *l*-menthone and *l*-methylurea possessed promising anticonvulsant activity when administered to mice. Subsequent clinical testing, however, showed that they were not useful for controlling convulsions in man.[1] Menthylurea is a very old compound, but the spirohydantoin from *l*-menthone was first reported in 1939.[2]

Tiffeneau and Beauvallet[3] reported that spirohydantoins prepared from cyclopentanone, cyclohexanone and cycloheptanone were ineffective against strychnine-induced spasms while those derived from isophorone and dihydroisophorone were effective. The spirohydantoins prepared from 3,5-dimethyl-, 3-ethyl-5-methyl-, 3-α-furyl-5-methyl- and 3-methyl-5-phenylcyclohexanone were reported to have little activity.[4]

In view of the unlikelihood that the compounds mentioned above are unique in possessing anticonvulsant action or even that they are the best possible compounds of this type, it was considered desirable to examine the effects of structure modification on activity. Most of the work reported here deals with the preparation of spirohydantoins from alkyl substituted cyclohexanones, for they were believed to be the most promising.

Camphorspirohydantoin had not been reported in the literature prior to the present study, although unsuccessful attempts to prepare it from camphor have been reported.[5] Camphorspirohydantoin was obtained in good yields when camphorimine was used in place of camphor as the starting material.

The use of optically active alkyl-substituted cyclohexanones naturally raises the question of whether isomerization occurs during hydantoin formation. This question has been considered, in the present investigation, only in the case of the spirohydantoin derived from *l*-menthone. *l*-Menthone, in which the methyl and isopropyl groups are in the *trans* configuration, might be expected to give two diastereoisomeric hydantoins. Since attempts to separate the spirohydantoin from *l*-menthone into diastereoisomeric modifications failed, all fractions melting at 228–229° and $[\alpha]^{24}D$ +11.7° (1.5% in ethanol), it seems likely that the spirohydantoin is a single individual and not a mixture.

Partial racemization of *l*-menthone by treatment with sulfuric acid[6] produced a mixture of *cis*- and *trans*-methylisopropylcyclohexanones, that is, *l*-menthone and *d*-isomenthone. This mixture of isomeric ketones was converted to the corresponding hydantoins. The latter were readily separated into two fractions by fractional crystallization from ethyl alcohol. The larger and more soluble fraction melted at 228–229° and was identical with the spirohydantoin from *l*-menthone. The smaller and less soluble fraction melted at 235.5–238.5°, $[\alpha]^{24}D$ +5.85° (2% in ethanol). Analyses indicated the compound to be isomeric with the spirohydantoin prepared from *l*-menthone. The second product must, therefore, be the isomer derived from the *d*-isomenthone.

An optically inactive methone from the Givaudan Corporation gave a spirohydantoin melting at 256.7–258.5°. No attempt was made to separate the product into isomeric forms.[7]

Experimental

***l*-3-*p*-Menthylamine.**—*l*-Menthone was prepared from *l*-menthol by chromic acid oxidation.[8] The ketone was converted to the corresponding oxime[9] and the latter reduced to the amine by the action of sodium and ethyl alcohol.[10] The amine was removed by steam distillation and collected in dilute hydrochloric acid. Evaporation gave 70–76%

(1) Private communication from Smith, Kline and French, Philadelphia, Pa.

(2) A. R. Day and C. F. Kelly, *J. Org. Chem.*, **4**, 101 (1939).

(3) R. Tiffeneau and M. Beauvallet, *Presse Med.*, **51**, 417 (1943).

(4) H. R. Henze, R. C. Wilson and R. W. Townley, THIS JOURNAL, **65**, 963 (1943).

(5) During the course of the present work, H. Hoyer [*Ber.*, **83**, 491 (1950)] reported the preparation of the spirohydantoin from both *d*-camphor and *dl*-camphor. He used the Bucherer procedure at elevated temperatures and pressures, yields 40–50%.

(6) E. Beckmann, *Ann.*, **250**, 335 (1889).

(7) This compound may be identical with the spirohydantoin prepared by Novelli [*Annales asoc. quim. Argentina*, **29**, 83 (1941); *C. A.*, **35**, 6576 (1941)]. He reported a m.p. of 257°.

(8) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., p. 340.

(9) E. Beckmann, *Ann.*, **250**, 325 (1889).

(10) R. L. Bateman and A. R. Day, THIS JOURNAL, **67**, 2496 (1935).

yields of the hydrochloride based on the menthol used, $[\alpha]^{26}D$ −36.6° (5% in water).

l-Menthylurea.—The method used previously[10] was modified considerably. To 65 g. of *l*-3-*p*-menthylamine hydrochloride in 150 ml. of water was added an equivalent of potassium cyanate (28 g.). The mixture was allowed to stand for 20 minutes and then warmed to 70° for 30 minutes. The resulting gummy solid, a mixture of *l*-menthylurea and *l*-menthylammonium isocyanate, was heated to just above the melting point for 5–10 minutes or until a quiet melt was obtained, whereby the isocyanate was converted to the urea. The *l*-menthylurea, obtained on cooling, was recrystallized from alcohol and water, yield 71.5%, m.p. 136.5–137.5°, $[\alpha]^{26}D$ −80.5° (2% in alcohol).

Spiro-(*p*-menthane-3,5'-hydantoin) or Menthonespirohydantoin).—The spirohydantoin from *l*-menthone was prepared by the Bucherer method as reported by Day and Kelly,[2] m.p. 227.9–229°, $[\alpha]^{24}D$ +11.7°. These values are somewhat higher than those reported previously.

1-*l*-(3-*p*-Menthyl)-hydantoin.—Ten grams (0.175 mole) of anhydrous glycolonitrile[11] was mixed with 25.3 g. of *l*-3-*p*-menthylamine. Heat was evolved and the solution separated into two layers. The crude N-*l*-(3-*p*-menthyl)-glycinonitrile (the oily layer) was converted to the crystalline hydrochloride by the addition of a slight excess of 20% hydrochloric acid. Crystallization is slow unless the solution is seeded. After filtration, the hydrochloride was washed with ether and dried. The hydrochloride was dissolved in water and treated with an equivalent of potassium cyanate. After stirring for 20 minutes, the mixture was heated at 70° for 30 minutes. The gummy solid was dissolved in 50 ml. of ethyl alcohol and 50 ml. of concentrated hydrochloric acid added. Slight warming caused the precipitation of fine crystals of 1-*l*-(3-*p*-menthyl)-hydantoin, yield 12.5%, m.p. 196–197°, $[\alpha]^{26}D$ −38.84° (1.2% in ethyl alcohol).

Anal. Calcd. for $C_{13}H_{22}O_2N_2$: C, 65.52; H, 9.31; N, 11.76. Found: C, 65.55; H, 9.11; N, 11.63.

1-*d*-Bornylhydantoin.—This compound was prepared from *d*-bornylamine by the procedure described above for 1-*l*-(3-*p*-menthyl)-hydantoin. In this case, the hydantoin separated in crystalline form after the N-*d*-bornylglycinonitrile hydrochloride in aqueous solution was heated with one equivalent of potassium cyanate at 70° for a short time, yield 50%, m.p. 194.6–196°, $[\alpha]^{25}D$ +3.3° (0.7% in ethyl alcohol).

Anal. Calcd. for $C_{13}H_{20}O_2N_2$: C, 66.07; H, 8.49; N, 11.86. Found: C, 66.24; H, 8.35; N, 11.96.

1-Cyclohexylhydantoin.—Twenty-five grams (0.25 mole) of cyclohexylamine and 14.2 g. (0.25 mole) of dry glycolonitrile were mixed with cooling. The N-cyclohexylglycinonitrile so obtained was dissolved in the calculated amount of dilute hydrochloric acid and an equivalent amount of potassium cyanate added gradually to the cold solution. After standing for one hour, the N-cyclohexyl-N-carbamidoglycinonitrile was removed, and washed with cold water and dried, yield 19.8 g., 44%. Ten grams of this material was dissolved in 50 ml. of ethyl alcohol and 50 ml. of hydrochloric acid added. After a short time 1-cyclohexylhydantoin separated, yield 9 g. (90%), m.p. 182.7–184.2°.

Anal. Calcd. for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.74; N, 15.38. Found: C, 59.17; H, 7.94; N, 15.37.

Spiro-(*p*-menthane-2,5'-hydantoin) or Carvomenthonespirohydantoin.—A commercial sample of carvone, *p*-menthadiene-1,8-one-6, b.p. 231°, $n^{23}D$ 1.4974, $[\alpha]^{23}D$ −3.16° (2% in ethyl alcohol), was used as starting material. Carvone (12.5 g.) in 80 ml. of dry ethanol was rapidly hydrogenated (10 minutes) at 50 lb. pressure using 2% palladium-on-alumina as catalyst. Only two equivalents of hydrogen were absorbed. The resulting carvomenthone could have contained only a small amount of carvacrol,[12] as indicated by the physical constants, $n^{23}D$ 1.4650°, $[\alpha]^{23}D$ −17.08° (3% in ethyl alcohol), and the high conversions to carvomenthonespirohydantoin. Carvomenthone was converted to the hydantoin by the method of Bucherer.[13] The mixture was heated at 52° for 10 hours, diluted with 800 ml. of water, allowed to stand for 2 hours and filtered. The crude product was dissolved in dilute sodium hydroxide solution and treated with decolorizing carbon. The hydantoin was then precipitated by the addition of dilute hydrochloric acid and recrystallized from alcohol, yield 80%, m.p. 233–234°, $[\alpha]^{24}D$ −0.10° (1% in ethyl alcohol).

Anal. Calcd. for $C_{12}H_{20}O_2N_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.09; H, 9.17; N, 12.36.

3,3,5,5-Tetramethylspiro-(cyclohexane-1,5'-hydantoin).—3,3,5,5-Tetramethylcyclohexanone was prepared by the 1,4-addition of methylmagnesium iodide to isophorone[14] and converted to the corresponding hydantoin by the Bucherer method, yield 85%, m.p. 276.7–277.7°.

Anal. Calcd. for $C_{12}H_{20}O_2N_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.23; H, 8.79; N, 12.56.

3-Isopropyl-5-methylspiro-(cyclohexane-1,5'-hydantoin).—3-Isopropyl-5-methyl-2-cyclohexen-1-one[15] was hydrogenated without a solvent at 50 lb. pressure with 2% palladium-on-alumina as catalyst. The resulting product, 3-isopropyl-5-methylcyclohexanone, was converted to the corresponding hydantoin by the Bucherer method. The crude product was dissolved in dilute sodium hydroxide solution, treated with decolorizing carbon and the hydantoin precipitated by saturating the solution with carbon dioxide. The dried product was dissolved in hot benzene and reprecipitated by the addition of petroleum ether, yield 70%, m.p. 212–216°.

Anal. Calcd. for $C_{12}H_{20}O_2N_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.50; H, 8.81; N, 12.50.

3-Hexyl-5-methylspiro-(cyclohexane-1,5'-hydantoin).—3-Hexyl-5-methyl-2-cyclohexen-1-one[15] was hydrogenated, as described above, to 3-hexyl-5-methylcyclohexanone, b.p. 276°. The latter was converted to the corresponding hydantoin by the Bucherer method, yield 80%, m.p. 193–195°.

Anal. Calcd. for $C_{15}H_{26}O_2N_2$: C, 67.71; H, 9.84; N, 10.59. Found: C, 67.85; H, 9.90; N, 10.57.

3',4'-Dihydrospiro-(hydantoin-5,1'-(2'H)-naphthalene) or α-Tetralonespirohydantoin.—This compound was prepared from α-tetralone by the Bucherer procedure. The crude product separated only after the reaction mixture was allowed to stand for one week. The crude product was recrystallized from hot alcohol by the careful addition of water, yield 30%, m.p. 237.2–238.2°.

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.60; N, 12.95. Found: C, 66.77; H, 5.48; N, 12.85.

This compound was prepared earlier by Novelli[7,16] who reported an 80% yield and a m.p. 237–239°.

Spiro-(hydantoin-5,3'-pinane) or Pinocamphonespirohydantoin.—β-Pinene, b.p. 55° at 15 mm., $[\alpha]^{24}D$ −14.3° (3% in ethyl alcohol), was oxidized with selenium dioxide according to the directions of Stallcup and Hawkins.[17] Two products were obtained, myrtenal, b.p. 62.8–63° at 2.2 mm., $[\alpha]^{24}D$ +0.90° (2% in ethyl alcohol), and pinocarvone, b.p. 74–74.5° at 5 mm., $[\alpha]^{24}D$ +61.6° (3% in ethyl alcohol). The pinocarvone was hydrogenated to pinocamphone using palladium-on-alumina as catalyst. After removing the catalyst, the reduced product was converted, without purification, to the corresponding spirohydantoin by the Bucherer method. After 8 hours of heating at 52°, the mixture was poured into water and allowed to stand until the oily layer solidified. The solid was removed and treated with petroleum ether to remove oily impurities. The residue was treated with a solution of dilute sodium hydroxide in ethyl alcohol and the insoluble material removed by filtration. Addition of hydrochloric acid to the filtrate produced a colorless precipitate which was recrystallized from alcohol, yield 20%. The compound decomposed above 300° but did not melt.

Anal. Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.61. Found: C, 65.04; H, 7.95; N, 12.70.

Spiro-(camphane-2,5'-hydantoin) or Camphorspirohydantoin.—*dl*-Camphor oxime (72 g.) was dissolved in 500 ml. of ether in a large separatory funnel. Sulfuric acid, 30

(11) Obtained from the American Cyanamid Company.

(12) R. S. Hughesdon, H. G. Smith and J. Read, *J. Chem. Soc.*, **123**, 2916 (1923); M. Busch and H. Stöve, *Ber.*, **49**, 1063 (1916).

(13) H. T. Bucherer and W. Steiner, *J. prakt. Chem.*, [2] **140**, 291 (1934).

(14) M. S. Kharasch and P. O. Tawney, THIS JOURNAL, **63**, 2308 (1941).

(15) Supplied by Dr. E. C. Horning.

(16) Novelli, *C. A.*, **37**, 2820 (1943).

(17) W. D. Stallcup and J. E. Hawkins, THIS JOURNAL, **63**, 3339 (1941); see also H. Schmidt, Schimmel's Report (1941), p. 6.

g. in 20% aqueous solution and 50 g. of sodium nitrite were added and the mixture was carefully shaken. As soon as the ether layer became deeply colored, it was transferred to a beaker where colorless crystals of camphorimine nitrate separated, yield 14.2 g., m.p. 144.5–145°. The melting point of camphorimine nitrate from *d*-camphor has been reported as 158–159°.[18]

Camphorimine nitrate, 8.5 g., 5 g. of potassium cyanide and 20 g. of ammonium carbonate in 200 ml. of 50% ethyl alcohol were heated at 52° for 5 hours. The camphorspirohydantoin separated in almost pure form. It was recrystallized from aqueous alcohol, yield 86%, m.p. 265.6–266.6°.

Anal. Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.61. Found: C, 64.92; H, 8.08; N, 12.54.

6',6'-Dimethylspiro-(hydantoin-5,2'-nopinone) or Nopinonespirohydantoin.—This hydantoin was prepared from nopinone[19] by the Bucherer procedure and recrystallized from alcohol and water, yield 75%, m.p. 275.7–276.5°, $[\alpha]^{31}D$ −15.00° (1% in ethyl alcohol).

Anal. Calcd. for $C_{11}H_{16}O_2N_2$: C, 63.43; H, 7.74; N, 13.45. Found: C, 63.35; H, 7.66; N, 13.25.

2-Δ'-Cyclohexenylspiro-(cyclohexane-1,5'-hydantoin).—2-Δ'-Cyclohexenylcyclohexanone was prepared from cyclohexanone.[20] The pure product boiled at 122° at 6 mm. Twenty grams of this ketone was dissolved in aqueous alcohol and treated by the Bucherer procedure. After 5 hours at 52°, the solution was poured into 800 ml. of water. After standing overnight, the oily crystals were removed, dissolved in alcohol and the non-acidic material precipitated by the addition of dilute sodium hydroxide solution. This mixture was heated with decolorizing carbon until a clear filtrate was obtained. The addition of dilute hydrochloric acid precipitated a reddish solid. The color was removed as follows: the solid was covered with a little benzene and, while warming, enough ethanol added to just dissolve the precipitate. A small amount of water was added to produce a second phase and a large excess of petroleum ether added to the warm mixture. The spirohydantoin separated as colorless crystals, while the aqueous layer retained the color, yield 6 g., m.p. 243–244°.

Anal. Calcd. for $C_{14}H_{20}O_2N_2$: C, 67.72; H, 8.03; N, 11.29. Found: C, 67.73; H, 8.12; N, 11.28.

2-Cyclohexylspiro-(cyclohexane-1,5'-hydantoin).—Cyclohexenylcyclohexanone was hydrogenated without a solvent using palladium-on-alumina as the catalyst. The resulting 2-cyclohexylcyclohexanone was converted to the corresponding spirohydantoin by the Bucherer method. The product was recrystallized from alcohol and water, yield 45%, m.p. 258–258.2°.

Anal. Calcd. for $C_{14}H_{22}O_2N_2$: C, 67.16; H, 8.83; N, 11.19. Found: C, 67.34; H, 8.99; N, 11.23.

5-(6,6-Dimethylbicyclo[3.1.1]-2-hepten-2-yl)-hydantoin.—Myrtenal (5.5 g.) was converted to the corresponding hydantoin by the Bucherer method. The product was recrystallized from 70% alcohol, yield 80%, m.p. 266.5–267°.

Anal. Calcd. for $C_{12}H_{16}O_2N_2$: C, 65.41; H, 7.32; N, 12.73. Found: C, 65.62; H, 7.16; N, 12.71.

5-(6,6-Dimethylbicyclo[3.1.1.]hept-2-yl)-hydantoin.—Myrtenal, 6.3 g., was hydrogenated to myrtanal in the presence of palladium-on-alumina. The myrtanal was then converted to the corresponding hydantoin by the Bucherer method. The crude product was dissolved in alcohol and a yellow, resinous material precipitated by the addition of dilute sodium hydroxide. Addition of hydrochloric acid to the filtrate gave the desired hydantoin. It was recrystallized from methanol, yield 75%, m.p. 229.5–231.5°.

Anal. Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.81; H, 8.16; N, 12.61. Found: C, 65.00; H, 8.07; N, 12.37.

3,3,5-Trimethylspiro-(cyclohexane-1,5'-hydantoin).—3,3,5-Trimethylcyclohexanecarboxaldehyde, 20.7 g.,[21] was converted to the corresponding hydantoin by the Bucherer method. It was recrystallized, with difficulty, from alcohol and water, yield 25%, m.p. 231.5°.

Anal. Calcd. for $C_{12}H_{20}O_2N_2$: C, 64.24; H, 8.99; N, 12.49. Found: C, 64.38; H, 8.70; N, 12.68.

1-*l*-Menthyl-5,5-diethylbarbituric Acid.—*l*-Menthylurea, 25 g., was condensed with ethyl diethylmalonate in dry ethanol with sodium ethoxide as catalyst. The alcohol was removed by slow distillation and the residue heated at 110–115° for 8 hours. The residue was shaken with 150 ml. of water and the two layers which formed were separated. The red oily layer was extracted with dilute hydrochloric acid and the extract added to the original aqueous layer. On standing for 24 hours, 4 g. of product separated. More was obtained by the slow evaporation of an alcoholic solution of the red oil. The total product was dissolved in dilute sodium hydroxide, filtered, reprecipitated with hydrochloric acid and recrystallized from alcohol, yield 12 g., m.p. 117–118°, $[\alpha]^{25}D$ −11.6° (2.5% in ethyl alcohol).

Anal. Calcd. for $C_{18}H_{30}O_3N_2$: C, 67.29; H, 9.21; N, 8.68. Found: C, 67.04; H, 9.38; N, 8.69.

1-Bornyl-5,5-diethylbarbituric Acid.—To 5 g. of sodium dissolved in dry ethanol was added 8.2 g. of *d*-bornylurea[11] and 9 ml. of ethyl diethylmalonate dissolved in ethanol. The alcohol was removed by slow distillation and the residue heated at 102° for 4 hours. The residue was worked up in the same way as described for the 1-menthylbarbiturate, yield 4 g., m.p. 136–136.5°, $[\alpha]^{28}D$ +8.60° (2.44% in ethyl alcohol).

Acknowledgment.—The authors with to express their appreciation to Leonard T. Capell, Associate Editor of Chemical Abstracts, for the nomenclature which he suggested and which was used in this paper.

PHILADELPHIA 4, PENNA.

(18) F. Tiemann, *Ber.*, **28**, 1080 (1895); F. Mahla and F. Tiemann, *ibid.*, **29**, 2807 (1896); J. Houben and E. Pfankuch, *ibid.*, **60**, 586, 595 (1927).

(19) O. Wallach, *Ann.*, **356**, 227 (1907); du Pont, *Bull. Inst. pin.*, 262 (1929).

(20) M. H. Gault, M. L. Daltroff and J. Ecktridon, *Bull. soc. chim.*, [5] **12**, 952 (1945).

(21) L. Givaudan et Cie (Soc. anon), French Patent 832,163, Sept. 22, 1938; H. Barbier, *Helv. Chim. Acta*, **23**, 519 (1940).