were obtained which could be recrystallized from dilute alcohol. Thus purified, **1,2-dihydro-2-keto-3-methylmercaptocinchoninic acid** (XIII) melts with decomposition at 219–220° (cor.).

Anal. Calcd. for $C_{11}H_9NO_3S$: neut. equiv., 235.3; N, 5.95; S, 13.63. Found: neut. equiv. (phenolphthalein), 238.9; N, 5.98; S, 13.84.

In the same manner, (VII) was converted into **1,2-dihydro-2-keto-3-methylmercapto-1-methylcinchoninic acid** (XIV), melting with decomposition at 229–230° (cor.).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: neut. equiv., 249.3; N, 5.62. Found: neut. equiv. (phenolphthalein), 245.4; N, 5.87.

From the dipotassium salt (IX) there was prepared a monopotassium salt which was recrystallized from 80% alcohol.

Anal. Calcd. for $C_{12}H_{10}KNO_3S$: N, 4.88; S, 11.16. Found: N, 5.00; S, 11.16.

A sample of this monopotassium salt was dissolved in water and treated with cold, dilute hydrochloric acid causing separation of a glistening yellow solid. After recrystallization from dilute alcohol, **1,2-dihydro-2-keto-3-methylmercapto-6-methylcinchoninic acid** (XV) was obtained as an orange crystalline material melting with decomposition at 221–222° (cor.).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: neut. equiv., 249.3; N, 5.62. Found: neut. equiv. (phenolphthalein), 246.2; N, 5.57.

Dimethyl sulfate converted the dipotassium salt XI into a monopotassium salt which did not melt at 300° and which did not give a positive test with Feigl reagent.[7]

Anal. Calcd. for $C_{13}H_{12}KNO_3S$: N, 4.65. Found: N, 4.35.

This salt upon acidification yielded yellow, crystalline material. Recrystallized from dilute alcohol, **1,2-dihydro-2-keto-3-methylmercapto-1,6-dimethylcinchoninic acid** (XVI) melts with decomposition at 224–225° (cor.).

Anal. Calcd. for $C_{13}H_{13}NO_3S$: neut. equiv., 263.3; N, 5.32. Found: neut. equiv. (phenolphthalein), 258.0; N, 5.61.

Reduction of 1,2-Dihydro-2-keto-3-methylmercaptocinchoninic Acids.—Six grams of XIII, 5 g. of red phosphorus and 50 cc. of hydriodic acid (sp. gr. 1.7) were refluxed for seven hours at 150°. After removal of the phosphorus by filtration and most of the acid by steam distillation, the solution was made alkaline with potassium hydroxide and then faintly acidic with hydrochloric acid; upon cooling, light yellow crystals (2 g. or 41% yield) were obtained. A mixture of this material with an authentic sample of **1,2,3,4-tetrahydro-2-ketocinchoninic acid** (XIX)[13] melted at 215–216° (cor.).

Anal. Calcd. for $C_{10}H_9NO_3$: N, 7.33. Found: N, 7.16.

Three grams of XIV was heated with 25 cc. of hydriodic acid and 2 g. of red phosphorus for eight hours at 150°, a gas with mercaptan-like odor being evolved. The gum which formed could not be caused to crystallize, but did not contain sulfur.

From heating a sample of XV with concentrated hydriodic acid for ten hours at 150° there was obtained white needles of **1,2,3,4-tetrahydro-2-keto-6-methylcinchoninic acid** (XX) melting at 219–220° (cor.). This melting point was not altered by mixture with an authentic sample.[14]

Anal. Calcd. for $C_{11}H_{11}NO_3$: N, 6.86. Found: N, 6.74.

Two attempts were made to reduce 1,2-dihydro-2-keto-3-methylmercapto-1,6-dimethylcinchoninic acid (XVI) with hydriodic acid alone or with red phosphorus; in neither case was it possible to secure a crystalline product.

Summary

The preparation of ketomercaptocinchoninic acids from rhodanine-($\Delta^{5,3'}$)-oxindoles has been studied. As a result it has been possible to synthesize examples of 1,2-dihydro-2-keto-3-methylmercaptocinchoninic acids, a type not previously reported in the chemical literature.

(13) Hill, Schultz and Lindwall [THIS JOURNAL, **52**, 773 (1930)] reported m. p. 217–218°.

(14) Henze and Blair, ref. 4.

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

Hydantoins Containing a Tetrahydropyranyl Substituent[1]

BY HENRY R. HENZE AND ROBERT L. MCKEE

Until quite recently, the clinical utilization of hydantoin derivatives had been limited wholly to the use of ethylphenylhydantoin (Nirvanol)[2] in the treatment of convulsions of the type of St. Vitus dance. However, the sodium salt of diphenylhydantoin (Dilantin)[3] has come now to be considered as virtually a specific for control of epileptic seizures. Treatment with this substituted hydantoin does not effect a cure of epilepsy, hence the necessity for further research seeking additional anticonvulsants.

A few hydantoin derivatives containing an alkoxy substituent[4] have been prepared in this Laboratory and shown elsewhere to possess vary-

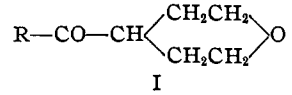
(1) Presented before the Medicinal Division of the American Chemical Society at Memphis, April, 1942.

(2) Swiss Patent 72,561 (Sept. 16, 1916).

(3) (a) Putnam and Merritt, *Science*, **85**, 526 (1937); (b) Merritt and Putnam, *J. Am. Med. Assoc.*, **111**, 1068 (1938); (c) Putnam, *ibid.*, **112**, 2190 (1939).

(4) (a) Rigler with Henze, THIS JOURNAL, **58**, 474 (1936); (b) Speer with Henze, *ibid.*, **61**, 3376 (1939); (c) Rogers and Henze, *ibid.*, **62**, 1758 (1940).

ing degrees of activity as anticonvulsants. A careful survey of the chemical literature fails to disclose evidence of the synthesis of any hydantoin possessing a cyclic ether grouping as a substituent. With these facts in mind, this research was begun with the intention to synthesize a series of cyclic keto ethers of the type (I) in which the —R grouping should be alkyl or phenyl, and, further, from these ketones to prepare a similar series of 5,5-disubstituted hydantoins of the type (II) in which the —R groupings should correspond to those of the parent ketones.



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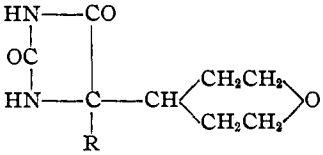

II

Only two examples of cyclic keto ethers (I) were known, namely, the methyl and ethyl tetrahydropyranyl ketones,[5] which were reported to be formed by action of the appropriate zinc alkyls upon the acid chloride of tetrahydropyran-4-carboxylic acid. In the present investigation, reaction of 4-cyanotetrahydropyran with appropriate Grignard reagents has been utilized in the resynthesis of these methyl and ethyl ketones, and in the initial preparation of six homologs and of the cyclohexyl and phenyl analogs. No appreciable quantity of ketone could be obtained from 4-cyanotetrahydropyran and either isopropylmagnesium bromide or *s*-butylmagnesium bromide.

Each of these ten acyl derivatives of tetrahydropyran has been converted into the corresponding hydantoin by interaction with potassium cyanide and ammonium carbonate in diluted alcohol solution. Through the courtesy of Parke, Davis and Company two of these new compounds, in the form of their sodium salts, have received preliminary pharmacological testing; 5-isoamyl-5-tetrahydropyranylhydantoin and its 5-phenyl analog were found to exhibit mild anticonvulsant activity and to be devoid of any hypnotic action.

Experimental

Ethyl 4-Cyanotetrahydropyran-4-carboxylate.—To a suspension of sodium ethylate, prepared from 31.5 g. of sodium and 450 cc. of absolute ethanol, was added 155 g. of ethyl cyanoacetate[6] followed by 97 g. of 2,2′-dichloroethyl ether. This mixture was heated under a reflux condenser for three hours and later allowed to stand for an additional twelve hours. After filtration from sodium chloride, the solution was fractionated and the material boiling 105–140° (16 mm.) was collected. Upon redistillation there was obtained 37 g. (31% yield) of ethyl 4-cyanotetrahydropyran-4-carboxylate boiling at 135° (16 mm.)[7]; $n^{20}D$ 1.4539; d^{20}_4 1.1109; y^{20} 37.4; *MR* calcd. 44.68; *MR* found 44.66; *P* calcd. 413.9; *P* found 407.9.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 58.95; H, 7.15; N, 7.65. Found: C, 58.77; H, 7.29; N, 7.71.

This ester was subsequently hydrolyzed by allowing a mixture of 32 g. of ester, 10.8 g. of potassium hydroxide, 9 cc. of water and 192 cc. of methanol to stand at room temperature for fifteen hours. Carbon dioxide was passed through the solution while the latter was concentrated on a water-bath. When solid matter began to separate it was redissolved and acidified with hydrochloric acid, causing separation of the organic acid. After recrystallization from the least amount of water, **4-cyanotetrahydropyran-4-carboxylic acid** (yield quantitative) melted at 163–164° (cor.).[8]

Anal. Calcd. for $C_7H_9NO_3$: neut. equiv., 155.1; N, 9.03. Found: neut. equiv. (phenolphthalein), 156.5; N, 9.12.

Tetrahydropyran-4-nitrile.—The carboxylic acid (28.5 g.) was heated under a reflux condenser in an oil-bath at 180–200° until evolution of carbon dioxide ceased. On fractionation of the residue, the nitrile distilled at 82–83° (10 mm.)[9] and left a small amount of solid product, which on further heating at 210–220° gave an additional amount of the nitrile. The total yield was 18.4 g. or 90%; $n^{20}D$ 1.4521; d^{20}_4 1.0343; y^{20} 40.7; *MR* calcd. 29.11; *MR* found 28.99; *P* calcd. 267.9; *P* found 272.0.

Preparation of Acyl 4-Tetrahydropyrans.—The ketones were prepared by addition of a molar proportion of tetrahydropyran-4-nitrile in absolute ether to 1.2–2.0 molar proportions of an appropriate Grignard reagent; the hydrolysis could be effected equally well with cold solutions of either ammonium chloride or hydrochloric acid. The ether extracts, after drying, were fractionated through an eight-inch (21 cm.) column containing a nichrome wire spiral. The purified ketones were water-white liquids having a sweet odor, and were miscible with ethanol or ethyl ether but immiscible with water. The compounds appear to be stable on standing and readily formed semicarbazones and 2,4-dinitrophenylhydrazones.

Preparation of 5-(4-Tetrahydropyranyl)-5-substituted Hydantoins.—A given ketone, together with 1.8 molar equivalents of potassium cyanide and 3.6 molar equivalents of ammonium carbonate (U. S. P. cubes), was dissolved in about 150 cc. of 50% ethyl alcohol and heated under a reflux condenser at 58–60° for twelve hours. The solution was evaporated to about one-half its original

(5) Prelog, Cerkovnikov and Heimbach, *Collection Czech. Commun.*, **10**, 399 (1938).

(6) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. I, 1932, p. 249.

(7) Gibson and Johnson [*J. Chem. Soc.*, 2528 (1930)] report b. p. 125° (16 mm.), but no other data.

(8) *Ibid.*, p. 2529, reported m. p. 160–162°.

(9) *Ibid.*, reported b. p. 82–83° (10 mm.).

TABLE I

4-ACYLTETRAHYDROPYRANS, R—CO—CH(CH$_2$CH$_2$)$_2$O

—R	Yield, %	B. p. °C. (cor.)	Mm.	$n^{20}D$	d^{20}_4	γ^{20}	Mol. refract. Calcd.	Found
Methyl[a]	53	205–207	144	1.4530	1.0243	35.8	33.98	33.84
Ethyl[b]	72	101	20	1.4541	1.0016	37.2	38.60	38.40
n-Propyl	57	85–88	5	1.4545	0.9828		43.22	43.08
n-Butyl	67	100	5	1.4551	.9700		47.83	47.61
Isobutyl	69	90–92	6	1.4545	.9648	33.2	47.83	47.83
n-Amyl	64	106–107	5	1.4573	.9589	33.3	52.45	52.39
Isoamyl	65	116–117	7	1.4567	.9562	32.9	52.45	52.46
n-Hexyl	61	134–135	6	1.4569	.9446		57.07	57.12
Cyclohexyl	46	142	5	1.4839	1.0262		54.87	54.72
Phenyl	67	57–58[c]						

—R	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Semicarbazone M. p., °C. (cor.)	2,4-Dinitrophenylhydrazone M. p., °C. (cor.)
Methyl	65.57	65.21	9.43	9.58	178	160–161[d]
Ethyl	67.55	67.28	9.92	10.08	151	146–147[e]
n-Propyl	69.18	68.87	10.32	10.54	145–146	
n-Butyl	70.54	70.21	10.66	10.68	180	99
Isobutyl	70.54	70.40	10.66	10.78	187–188	122
n-Amyl	71.69	71.39	10.94	10.95	117	89–90
Isoamyl	71.69	71.60	10.94	10.93	158–159	134–135
n-Hexyl	72.68	72.67	11.18	11.19	161	
Cyclohexyl	73.42	73.43	10.27	10.19	213–214	
Phenyl	75.76	75.62	7.42	7.65		(*f*)

[a] Prelog, Cerkovnikov and Heimbach, ref. 5, reported b. p. 90–94° (15 mm.); we found b. p. 91–92° (15 mm.). [b] *Ibid.*, reported b. p. 103° (15 mm.). [c] M. p. of the solid ketone. [d] Prelog, Cerkovnikov and Heimbach, ref. 5, reported m. p. 160.0–160.5°. [e] *Ibid.*, reported m. p. 146.0–146.5°. [f] Did not form; the ketone was recovered unchanged.

TABLE II

HYDANTOINS CONTAINING A TETRAHYDROPYRANYL SUBSTITUENT

HN—CO(R)—C—CH(CH$_2$—CH$_2$)$_2$O—CH—NH—CO

—R	M. p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
Methyl	250	51	54.53	54.79	7.12	7.30	14.13	14.14
Ethyl	246	70	56.59	56.25	7.60	7.69	13.20	13.34
n-Propyl	223	66	58.39	58.41	8.02	8.18	12.38	12.19
n-Butyl	195	49	59.98	59.74	8.39	8.48	11.66	11.60
Isobutyl	222	53	59.98	59.76	8.39	8.50	11.66	11.55
n-Amyl	171–172	79	61.39	61.30	8.72	8.74	11.02	11.15
Isoamyl	195–196	68	61.39	61.22	8.72	8.77	11.02	10.97
n-Hexyl	169	48	62.66	62.58	9.01	9.04	10.48	10.61
Cyclohexyl	304–306	65	63.12	63.01	8.33	8.40	10.52	10.63
Phenyl	253	72	64.57	64.23	6.20	6.39	10.77	10.88

volume and then was acidified with hydrochloric acid causing separation of the hydantoin. In general, two recrystallizations from 20% alcohol produced crystalline white material, seemingly quite insoluble in water, but readily soluble in alkaline solution. Sodium salts of the hydantoins could be prepared readily by addition of the calculated amount of sodium ethylate to an alcoholic solution of the hydantoin and evaporation to dryness.

Summary

1. Eight new cyclic ether ketones, containing the tetrahydropyran nucleus, have been prepared.

2. The initial synthesis is reported of ten examples of a novel type of hydantoin containing a cyclic ether (tetrahydropyranyl) grouping.

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