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

SYNTHESIS OF 5-(PYRIDYL-SUBSTITUTED)HYDANTOINS[1]

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The results of pharmacological investigations, chiefly by Merritt and Putnam (1), have clearly demonstrated that several 5-substituted hydantoins possess distinct activity as anticonvulsants and, indeed, two such derivatives, 5,5-diphenylhydantoin and 5-ethyl-3-methyl-5-phenylhydantoin, are in clinical use. The success of the latter has created some impression that only those hydantoins having at least one 5-phenyl group substituent are likely to exhibit anticonvulsant activity (2). Since it is rather commonly held that great similarity as to "aromatic character" exists between benzene and pyridine,[3] it seemed of interest to synthesize some 5-pyridyl-substituted hydantoin derivatives in order to permit evaluation elsewhere of the latter.

Previously, there had been reported only a few 5-alkyl-5-(3-pyridyl)hydantoins (3), and but one other pyridylhydantoin, namely, 5-phenyl-5-(2-pyridyl)-hydantoin.[4, 5] Since the 5-alkyl-5-phenylhydantoins in several instances have been found to have strong anticonvulsant activity (1), it was decided to attempt the synthesis of a series of 5-alkyl-5-(2-pyridyl)hydantoins. Also, it seemed desirable to prepare certain of the isomeric 5,5-dipyridylhydantoins so that their respective activities might be subsequently determined for comparison with that of the isosteric 5,5-diphenylhydantoin. In order to make the series more nearly complete, the three, isomeric 5-pyridylhydantoins were produced in order to permit their pharmacological evaluation and comparison with that of 5-phenylhydantoin. For the preparation of these 5-pyridylhydantoins, the three, isomeric pyridinemethanals were resynthesized. However, a superior synthesis of 4-pyridinemethanal was developed through oxidation of 4-methylpyridine with freshly prepared selenium dioxide. It was found necessary to convert these

[1] From the Ph.D. dissertation of M. B. Knowles, The University of Texas, May, 1949.

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[3] Concerning the similarity of benzene and pyridine as to "Aromatic Character", it may be pointed out that Mosher [*Heterocyclic Compounds*, Elderfield, John Wiley and Sons, Inc., New York, 1950, p. 402] has called attention to the typical "aromatic" nature of the 3-(or β-position) in pyridine and to the "anomalous" nature of the 2- and 4-(or α and γ) positions. In addition, it must be appreciated that in respect to its weakly basic nature, pyridine is quite different from benzene in chemical behavior and solubility. Therefore, it is unwise to prophesy *pharmacological* activity solely upon a basis such as limited similarity in "aromatic character".

[4] This potent anticonvulsant drug was presented initially in the Ph.D. dissertation of Leslie G. Nunn, Jr., The University of Texas, June, 1943, p. 58. More recently, this same compound was reported by Teague, *J. Am. Chem. Soc.*, **69**, 714 (1947).

[5] Likewise, in this laboratory phenyl 3-pyridyl ketone had been converted into 5-phenyl-5-(3-pyridyl)hydantoin (m.p. 228–230°) and into the hydrochloride of the latter (m.p. 255–257° with dec.); *cf.* Ph.D. dissertation of Wm. Josiah Clegg, The University of Texas, June, 1947. This hydantoin evidences a high degree of anticonvulsant activity.

aldehydes into their sodium bisulfite-addition products before conversion into hydantoins.

Of the ten alkyl 2-pyridyl ketones needed for conversion into 5-alkyl-5-(2-pyridyl)hydantoins, only three, having *n*-alkyl groups, had previously been prepared. Of the seven new ketones, six contain branched-chain alkyl groups. Except for the first two members of this series, the carbonyl compounds were synthesized by means of the interaction of the appropriate alkylmagnesium bromide and 2-cyanopyridine.[6]

None of the dipyridyl ketones has previously been reported in the literature. All of the possible combinations, except 4,4′-dipyridyl ketone, were synthesized by bringing together a pyridyllithium and a cyanopyridine at −35°;[7] the preparation of the 4,4′-dipyridyl ketone was not attempted due to the instability of 4-bromopyridine. All five of these dipyridyl ketones were converted into 5,5-dipyridylhydantoins.

Certain of the 5-alkyl-5-(2-pyridyl)hydantoins were isolated in two forms, possibly diastereoisomers, which differed in melting points, crystal appearance, and solubilities. These instances are those in which the branched chain alkyl group (a) suffers hindered rotation and (b) the tertiary carbon of the branched alkyl lacks symmetry. Infrared absorption spectra of the higher-melting and lower-melting forms of a given hydantoin were very similar. In an attempt to obtain more information concerning these compounds, a mixture of the higher-melting and lower-melting forms of 5-(1-methylpropyl)-5-(2-pyridyl)hydantoin was subjected to the action of boiling barium hydroxide solution. The product isolated, 2-methyl-1-(2-pyridyl)butylamine, was not the expected amino acid.

EXPERIMENTAL

Preparation of pyridinemethanals. Following the procedure of Lenart (4), 2-methylpyridine was condensed with benzaldehyde and the resulting 2-styrylpyridine was ozonized to yield 2-pyridinemethanal, which was purified as its sodium bisulfite-addition product; the latter could be used in the preparation of the hydantoin. For the production of 3-pyridinemethanal, nicotinic acid was converted through the acid chloride into the hydrazide. The latter was treated with benzenesulfonyl chloride, and the product was heated in ethylene glycol solution with sodium carbonate to yield the aldehyde (5, 6). Although Wibaut (7) had prepared 4-pyridinemethanal from ozonolysis, we prefer to produce it as a result of the direct oxidation of 4-methylpyridine with selenium dioxide.

To freshly prepared selenium dioxide (143 g.; 1.29 moles) and 1,4-dioxane (800 ml.) was added 4-methylpyridine (119 g.; 1.29 moles); a deep red solid formed almost immediately. The temperature of the stirred mixture was raised to reflux temperature for two hours; the color of the solid changed to grayish-black and that of the solution to light orange. After

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[6] This procedure is superior to that of Pinner [*Ber.*, **34,** 4234 (1901)] who synthesized the three lowest members of the alkyl 2-pyridyl ketone series through Claisen condensation of ethyl picolinate and ethyl acetate; the condensation product was hydrolyzed to yield the methyl ketone. However, if the condensation product was methylated or ethylated before hydrolysis, the corresponding higher alkyl (ethyl or propyl) ketone could be obtained.

[7] This appears to be the first use of 3-pyridyllithium in any reaction other than carbonation, and the first preparation of 2-pyridyllithium; the publication by Wibaut, de Jonge, van der Voort, and Otto appeared nearly two years later in *Rec. trav. chim.*, **70,** 1054 (1951); *Chem. Abstr.*, **46,** 11,197 (1952).

TABLE I

ALKYL 2-PYRIDYL KETONES, $RCOC_5H_4N$

R—	FORMULA	B.P., °C.	MM.	YIELD, %	n_D^{25}	d_4^{20}	MOLEC. REFRACT.		C		H	
							Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_3[a]	C_7H_7NO	190	754									
CH_2CH_3[b]	C_8H_9NO	73	5	40								
$CH_2CH_2CH_3$[c]	$C_9H_{11}NO$	116–117	25	70								
$CH(CH_3)_2$[d]	$C_9H_{11}NO$	107–108	25	82	1.5028	1.0140	42.59	43.47	72.45	72.20	7.43	7.42
$CH_2CH_2CH_2CH_3$[e]	$C_{10}H_{13}NO$	129–130	25	81	1.5023	1.0011	47.21	48.16	73.58	73.40	8.03	8.19
$CH(CH_3)CH_2CH_3$[f]	$C_{10}H_{13}NO$	120–122	25	86	1.5009	0.9989	47.21	48.14	73.58	73.36	8.03	8.18
$CH_2CH(CH_3)_2$[g]	$C_{10}H_{13}NO$	122–123	25	88	1.4998	.9964	47.21	48.17	73.58	73.34	8.03	8.31
$C(CH_3)_3$[h]	$C_{10}H_{13}NO$	108–110	25	46	1.5000	1.0057	47.21	47.73	73.58	73.34	8.03	8.33
$CH(CH_3)CH_2CH_2CH_3$[i]	$C_{11}H_{15}NO$	132–133	25	56	1.4978	.9834	51.80	52.83	74.54	74.46	8.53	8.66
$CH(CH_2CH_3)_2$[j]	$C_{11}H_{15}NO$	130	25	43	1.4992	.9847	51.80	52.87	74.54	74.43	8.53	8.66

[a] M.p. of *phenylhydrazone* 154.5°; Engler and Rusumoff, *Ber.*, **24**, 2827 (1891) reported m.p. 155°. [b] Pinner, *Ber.*, **34**, 4234 (1901) reported b.p. 205°. *Phenylhydrazone*, m.p. (141–142°), checked that reported by Engler and Bauer, *Ber.*, **24**, 2530 (1891). [c] M.p. of *phenylhydrazone* and *oxime* respectively 83.4–86.5° and 46–48°; Engler and Majmon, *Ber.*, **24**, 2536 (1891) reported m.p. of *phenylhydrazone* and *oxime* respectively as 82° and 48°. [d] M.p. of *semicarbazone* 140–142°; m.p. of *2,4-dinitrophenylhydrazone* 181.0–181.5°. [e] M.p. of *semicarbazone* 145–146°; m.p. of *2,4-dinitrophenylhydrazone* 135–136°. [f] M.p. of *semicarbazone* 122–123°; m.p. of *2,4-dinitrophenylhydrazone* 166°. [g] M.p. of *semicarbazone* 151.0–152.5°; m.p. of *2,4-dinitrophenylhydrazone* 156–157°. [h] M.p. of *2,4-dinitrophenylhydrazone* 195.0–195.5°; m.p. of *phenylhydrazone* 98–99°. [i] M.p. of *2,4-dinitrophenylhydrazone* 159–162°. [j] M.p. of *semicarbazone* 86–88°; m.p. of *2,4-dinitrophenylhydrazone* 175.5–176.0°.

cooling, the mixture was filtered. The filtrate was treated with 120 ml. of concentrated hydrochloric acid and evaporated to dryness *in vacuo* at 35°. The residue was covered with 25 ml. of water and 100 g. of sodium carbonate and the mixture was subjected to steam-distillation. The distillate was collected (approximately 600 ml.) until it failed to give a silver mirror with Tollen's reagent. The distillate was acidified and concentrated to 150 ml. *in vacuo*. The concentrate was saturated with potassium carbonate and extracted with ether. The extract was dried with sodium sulfate and was warmed to remove ether; the residue (66 g.) contained some 4-methylpyridine.

The crude product was poured into 200 ml. of sodium bisulfite solution containing 50 g. of this salt. Sulfur dioxide was bubbled into this solution; white crystalline material separated and was removed and washed with a small quantity of alcohol. The bisulfite product (25.5 g.; 10.5% yield) melted with sublimation at 218°, and yielded a solid, yellow phenylhydrazone, m.p. 178–179°.[8] Actually, this sodium bisulfite-addition product, rather than the regenerated aldehyde, was used to prepare 5-(4-pyridyl)hydantoin.

Preparation of alkyl 2-pyridyl ketones. The first two members of this series were made by the method of Pinner (8) utilizing a crossed Claisen type condensation between ethyl picolinate and ethyl acetate; hydrolysis and decarboxylation of the product produced methyl 2-pyridyl ketone, but methylation of the condensation product, with subsequent hydrolysis and decarboxylation, led to the ethyl ketone. However, due to the length of the preparation and to the physical properties of the sodio derivative of ethyl 2-pyridoylacetate, this method was discarded in favor of the reaction between 2-cyanopyridine and the appropriate Grignard reagent. The required cyanopyridine was obtained through interaction of cuprous cyanide and 2-bromopyridine (the latter was formed by diazotization of 2-aminopyridine in the presence of concentrated hydrobromic acid). The properties of the alkyl 2-pyridyl ketones prepared are collected in Table I.

[8] These data correspond to those of the product obtained by the method of Wibaut, Kooyman, and Boer [*Rec. trav. chim.*, **64**, 30 (1945)], who utilized ozonolysis of 4-styrylpyridine. The procedure here outlined is far simpler, more rapid and better suited to preparation of larger amounts of 4-pyridylmethanal.

TABLE II

DIPYRIDYL KETONES, RCOR'

R—	R'—	M.P., °C.	YIELD, %	N		SEMICARBAZONE			2,4-DINITROPHENYLHYDRAZONE M.P., °C.
				Calc'd	Found	M.P., °C.	N Calc'd	N Found	
2-Pyridyl	2-Pyridyl	53.5–54.0	42	15.21	15.04	219–220	29.03	29.05	250–251 (dec.)
2-Pyridyl	3-Pyridyl	72	10	15.21	15.24	156.5–157.5			233.0–233.5 (dec.)
2-Pyridyl	4-Pyridyl	122–123	80	[a]		237–239			219[c]
3-Pyridyl	3-Pyridyl	117–118	11	15.21	15.42	196–197 (dec.)			168.0–168.5[d]
3-Pyridyl	4-Pyridyl	124.0–124.5	21	[b]		227.5 (dec.)			176.5–177.5[c]

[a] Calc'd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38. Found: C, 71.73; H, 4.30. [b] Calc'd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38. Found: C, 71.68; H, 4.48. [c] M.p. of oxime. [d] M.p. of phenylhydrazone.

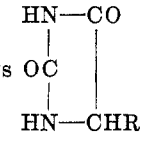
Preparation of the dipyridyl ketones. The procedure used was to bring together the appropriate pyridyllithium and a cyanopyridine. For the preparation of the pyridyllithiums, Gilman's method (9), involving interaction of butyllithium and a bromopyridine, was utilized. Butyllithium was obtained through the improved procedure of Gilman (10) using 1-bromobutane or 1-chlorobutane. In a typical experiment, 4.2 g. (0.6 g.-atom) of lithium wire, cut into 300 pieces, was placed in a flask provided with reflux condenser mechanical stirrer, and a dropping-funnel; all openings were protected as for a Grignard reaction. The lithium was covered with 250 ml. of anhydrous ether, and 42 g. (0.3 mole) of 1-bromobutane, contained in 50 ml. of dry ether, was added dropwise over a period of 4–5 hours. Finally, the ether was refluxed for 30 minutes. The solution contained about 0.15 mole of butyllithium. Although all of the lithium had not reacted, it was found not to interfere if care was used in decomposition of the reaction mixture.

The reaction flask was cooled in a large metal vessel containing acetone or methanol to which pieces of Dry Ice were added until the temperature fell to about −55°. While maintaining the temperature between −55° and −45°, 23.7 g. (0.15 mole) of the appropriate bromopyridine, dissolved in 50 ml. of dry ether, was added over a period of 5 minutes.[9] After addition of the halide, the reaction mixture was stirred for 15 minutes at a bath temperature between −50° and −40° before 15.6 g. (0.15 mole) of a cyanopyridine, dissolved in 50 ml. of ether, was added during about 15 minutes. Stirring was again continued for 15 minutes, the temperature being maintained below −30°. The final reaction mixture contained much solid material, which was either orange-red or blood-red, but was easily stirred. Decomposition was effected by adding 100 ml. of hydrochloric acid (containing 0.5 mole of hydrogen chloride). The unreacted lithium floated on top of the ether layer which was separated quickly from the acid portion with a separatory-funnel. The ether solution was drained through the stopcock to leave the unreacted lithium. The ether extract was treated once with 20 ml. of dilute acid and the latter was combined with the original acidic layer; a dark red color always was prominent. Addition of concentrated ammonium hydroxide solution caused separation of a dark oil or solid; the purification of the crude ketone product was accomplished in appropriate manner. Data concerning the five dipyridyl ketones prepared have been placed in Table II.

[9] A change in color was observed with each bromo derivative used. The color was light yellow when 3-bromopyridine was utilized, and blood-red with 2-bromopyridine.

TABLE III

5-PYRIDYL-SUBSTITUTED HYDANTOINS



R—	YIELD, %	M.P., °C.	C		H	
			Calc'd	Found	Calc'd	Found
2-Pyridyl.....	81	243.5 (dec.)	54.23	54.03	3.98	4.05
3-Pyridyl.....	88	223 (dec.)	54.23	54.39	3.98	4.28
4-Pyridyl.....	40	304 (dec.)	54.23	54.25	3.98	3.99

Preparation of 5-pyridylhydantoins. The sodium bisulfite-addition product of a pyridinemethanal in 50% alcohol was heated with potassium cyanide (2.25 mole-equivs.) and ammonium carbonate (4.5 mole-equivs.) at 50–55° for 4 to 6 hours, then at 80–90° for 30 to 60 minutes. The volume of the reaction mixture was reduced to about one-fourth by evaporation. Usually, solid material separated, otherwise the product was obtained by acidification with acetic acid. In some cases, adequate purification could be obtained as a result of dissolving the crude 5-pyridylhydantoin in 5% sodium hydroxide solution and reprecipitating the hydantoin by acidification; the latter could be accomplished by addition of solid carbon dioxide. The snow white 3-pyridyl compound was finally recrystallized from water. The bright yellow 2-pyridyl derivative was recrystallized with more difficulty from water or ethylene glycol. The crude 4-pyridyl isomer was definitely a yellow crystalline solid and was the least soluble of the three deviratives; it was recrystallized from methanol as a light cream-yellow solid. Data for these three hydantoins appear in Table III.

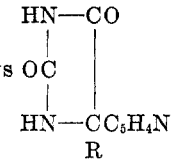
Preparation of 5-alkyl-5-(2-pyridyl)hydantoins. To prepare these compounds, a mixture of 0.1 mole of an alkyl 2-pyridyl ketone in 100 ml. of ethyl alcohol, 0.2 mole of potassium cyanide dissolved in 100 ml. of water, and 0.4 mole of ammonium carbonate was warmed from room temperature to about 60° during a period of 2 hours, and then was maintained at 60° for 12–24 hours. In most cases, a deep red-wine color developed. Alternately, the reaction mixture was heated in a closed container at 110° for 8 hours. After evaporation of much of the solvent, the residue was neutralized with hydrochloric acid and the precipitated hydantoin was redissolved in 5% alkaline solution and reprecipitated by exact neutralization. Final purification was effected by recrystallizations from diluted alcohol. Pertinent data for these hydantoins may be found in Table IV.

Certain of these 5-alkyl-5-(2-pyridyl)hydantoins were obtained in two forms which differed in melting point and in solubility, but were identical in composition, and could not be interconverted by seeding the molten materials. These possible diastereisomers have been designated as the lower-melting form and the higher-melting form. Although the presently available atomic models for nitrogen do not fit well into molecular models for nitrogen-heterocycles, models of these hydantoins indicate hindered rotation of alkyl groups about the α-carbon atom of the 5-alkyl substituent. When the two sub-groups are not identical, as in $-CH(CH_3)C_2H_5$, the degree of restricted rotation appears to warrant two limiting positions of the *sec*-butyl substituent.

Determination of infrared absorption spectra. The infrared absorption spectra were determined witha Beckman Infrared Spectrophotometer. The samples were prepared by making a paste of a small amount of the hydantoin with Nujol and the absorption was determined for the higher-melting form and the lower-melting form of 5-(1-methyl-propyl)-5-(2-pyridyl)hydantoin. These two forms were almost identical in wave length of absorption, one exception being the corresponding peaks which occur at 7.13 and 7.32 microns for the higher- and lower-melting forms, respectively. These are in the region of $-CH_3$ and

TABLE IV

5-ALKYL-5-(2-PYRIDYL)HYDANTOINS



R—	YIELD, %	M.P., °C.	N		C		H	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
Methyl	41	171.0–171.5	21.98	21.98				
Ethyl	88	184–185	20.47	20.33				
Propyl	90	155.0–156.5	19.17	19.38				
1-Methylethyl	98	246.5–248.0	19.17	19.39				
Butyl	93	167.5–168.0	18.03	18.00				
2-Methylpropyl	65	144.0–145.5[a]	18.03	18.26				
1-Methylpropyl	89	190–219[b]						
higher-melting form		231–233	18.03	17.68	61.78	61.62	6.48	6.50
lower-melting form		185–188	18.03	18.39	61.78	61.56	6.48	6.54
1,1-Dimethylethyl	41	266.5–267.0 (dec.)	18.03	18.08				
1-Methylbutyl	96	140–159[c]	16.99	17.17				
higher-melting form		233–234						
lower-melting form		140–144	16.99	16.97				
third form		185–186						
1-Ethylpropyl	76	140 and 167[d]	16.99	17.26				

[a] The reaction product melted at 138–145°. Recrystallization twice from diluted alcohol raised the m.p. to 139–146°; however, although the sample began to form liquid in the m.p. tube at 139°, it seemed partially to resolidify before complete fusion at 146°. Upon cooling and resolidification, the solid remelted sharply at 146°. The m.p. here reported is that of such material after recrystallization from benzene.

[b] The reaction product was dissolved in 5% sodium hydroxide solution and reprecipitated by acidification. This product was recrystallized once from 95% ethyl alcohol and nine times from more dilute alcohol to yield the *higher-melting form* of this hydantoin. A second crop of crystals was obtained from the mother liquor of the first recrystallization; after four recrystallizations from diluted alcohol there was obtained the *lower-melting form* of this hydantoin.

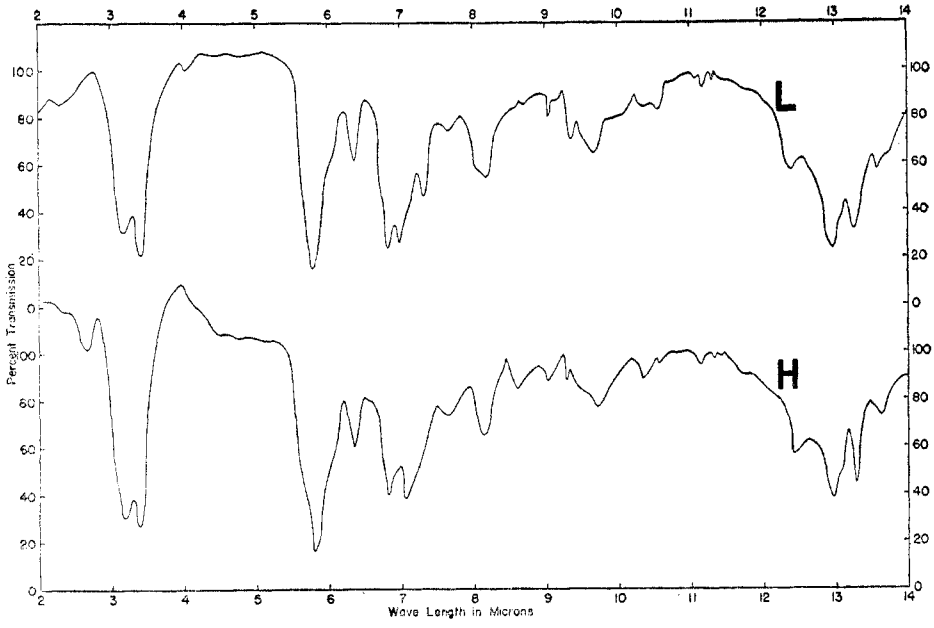
[c] This product was recrystallized nine times from dilute alcohol; a material, melting at 184–200°, was obtained which, when examined under a microscope, appeared to consist of two different types of crystals. In an attempt to effect separation, the material was crystallized from benzene producing solid (S) and filtrate (F). The solid (S) was crystallized three times from dilute alcohol to yield a homogeneous crystalline mass melting at 233–234°.

The filtrate (F) was concentrated and chilled to give crystalline material melting at 184–186° and a filtrate (F2). After four additional recrystallizations the product appeared homogeneous and melted at 185–186°.

From the filtrate (F2) was obtained a crystalline residue melting at 140–144°. Successive recrystallizations failed to produce a constant melting material, but merely caused a broadening in m.p. with rise in range.

[d] When heated rapidly, this product melted at 140°, resolidified about 150°, and fused at 166–167°. When heated slowly, initial fusion took place at 140°; resolidification was complete at 150°, and final melting occurred at 166–167°. Repeated recrystallizations from diluted alcohol or from benzene caused no change in m.p. behavior. The m.p. of fused and resolidified product was 167°.

Fig. 1- Infrared absorption spectra of 5-(1-methylpropyl)-5-(2-pyridyl) hydantoin: L, low-melting variety; H, high-melting variety.



—CH_3 vibrations. The two spectrograms, Fig. 1, are what might be expected from isomers differing in crystal structure, but the variation in peaks does not exclude the possibility of differences in orientation of the *sec*-butyl grouping.

Hydrolysis of 5-(1-methylpropyl)-5-(2-pyridyl)hydantoin. The reaction mixture (5 g.) containing both the higher and lower-melting forms of this hydantoin was refluxed for 13 days with 60 ml. of 30% barium hydroxide solution. Liberation of ammonia was noted after approximately hour hours of heating and it continued over most of the total time of the refluxing. The reaction mixture was cooled and made slightly acidic by addition of dilute sulfuric acid. The barium sulfate was removed and the filtrate was brought to *p*H 7 by addition of dilute barium hydroxide solution. The mixture was evaporated to dryness and the residue was extracted with hot 95% ethyl alcohol. After decolorization of the extract, it was concentrated by evaporation before being poured into a large volume of ether; a grayish solid material separated. The filtrate from this solid was evaporated to dryness and yielded less than 1 ml. of residue. The grayish solid was recrystallized from a methanol-ether mixture to yield a white, crystalline material melting at 140.0–142.5°.

Anal. Calc'd for $C_{11}H_{16}N_2O_2$: N, 13.45. Found: N, 13.35.

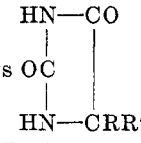
An attempt was made to carry out a Sorensen formol titration, but the addition of barium hydroxide solution produced formation of a white solid and an oily liquid of fishy odor. The solid material was then found to contain sulfur in the form of sulfate thus suggesting the product to be an amine sulfate.

Anal. Calc'd for $C_{20}H_{34}N_2O_4S$: N, 13.14; S, 7.52.
Found: N, 13.35; S, 7.5.

Since the values for nitrogen and sulfur agreed well with the values calculated for these elements in the diamine sulfate which might have resulted from decarboxylation of the α-amino acid anticipated from hydrolysis of the hydantoin, the product was dissolved in dilute sodium hydroxide solution; an oily liquid appeared and was extracted with ether; the extract was treated with phenyl isothiocyanate to produce a white solid. After purification the product was analyzed.

TABLE V

5,5-DIPYRIDYLHYDANTOINS



R—	R'—	YIELD, %	M.P., °C.	C		H		N	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
2-Pyridyl	2-Pyridyl	34	257–258 (dec.)[a]	61.41	61.14	3.99	4.19	22.04	22.15
2-Pyridyl	3-Pyridyl	48	243–244 (dec.)	61.41	61.19	3.99	3.98		
2-Pyridyl	4-Pyridyl	89	215.5–216.0	61.41	61.36	3.99	4.14		
3-Pyridyl	3-Pyridyl	54	214–215	61.41	61.01	3.99	4.33	22.04	22.04
3-Pyridyl	4-Pyridyl	41	213–214[b]	61.41	61.18	3.99	4.12		

[a] When heated rapidly, this di(2-pyridyl)hydantoin melted at 263° (dec.). [b] A mixture of this hydantoin and its 2-pyridyl-4-pyridyl isomer (m.p. 215.5–216.0°) melted at 206°.

Anal. Calc'd for $C_{17}H_{21}N_3S$: N, 14.04. Found: N, 14.32.

Preparation of 5,5-dipyridylhydantoins. These disubstituted hydantoins,[10] too, were obtained through interaction of the dipyridyl ketones with potassium cyanide and ammonium carbonate in approximately 50% alcohol at 60° for periods of 12–24 hours. Purification of these hydantoins required individual studies to ascertain satisfactory choices of solvents if separation of oily products rather than crystalline materials was to be avoided. Data concerning these hydantoins appear in Table V.

SUMMARY

The three isomeric 5-substituted hydantoins containing a 2-, 3-, or 4-pyridyl substituent have been prepared. Of the 5,5-disubstituted hydantoins, those possessing the 2,2'-, 2,3'-, 2,4'-, 3,3'-, or 3,4'-dipyridyl substituents have been synthesized. In addition, seven members of the 5-alkyl-5-(2-pyridyl)hydantoin series have been obtained.

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[10] The ease of conversion of the dipyridyl ketones into 5,5-pyridylhydantoins is in sharp contrast to the difficulty with which diphenyl ketone (benzophenone) is converted into the isosteric 5,5-diphenylhydantoin; the latter conversion requires heating at 60° for about one week, although at 140° a few hours suffice. The quite marked difference in reactivity of these two types of ketones does not justify the concept of their similar "aromatic character".

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