and co-workers[22] report for D-lyxonamide: m. p. 110°; $[\alpha]^{20}D$ −13.5° (*c* 1, water).

The crude, finely powdered D-lyxonamide was acetylated, in 50-g. portions, by stirring for eight hours at 0° with 365 g. of acetic anhydride containing 20 g. of zinc chloride. The temperature of the mixture was then allowed to rise to room temperature and maintained there until all of the amide was in solution whereupon it was poured into 1 liter of ice and water and allowed to stand for three hours with occasional stirring. The solution was extracted with six 100-ml. portions of chloroform. The combined chloroform extract was washed once with water, dried with anhydrous sodium sulfate and concentrated to a sirup. This sirup has failed to crystallize and was used directly in the next step.

The above sirup (from 50 g. of D-lyxonamide), following the general deamination procedure of Hurd and Sowden,[6] was dissolved in five times its weight of glacial acetic acid and divided into 50-ml. portions. Oxides of nitrogen, generated by the action of concentrated sulfuric acid on sodium nitrite, were bubbled into the acetic acid solutions until a dark green color persisted whereupon the flow of gas was stopped and the solutions were allowed to stand at room temperature for four hours. The combined acetic acid solution was evaporated under reduced pressure at 50° to a sirup. The sirup was dissolved in an excess of aqueous sodium bicarbonate and extracted with chloroform, the extract being discarded. The bicarbonate solution was then acidified with dilute hydrochloric acid and again extracted several times with chloroform. The combined chloroform extract was dried with anhydrous sodium sulfate and concentrated again to a thick sirup. The last traces of chloroform were removed by distilling the sirup with toluene under reduced pressure. The sirup was crystallized from toluene; yield 84.5 g. from 100 g. of D-lyxono-γ-lactone. Three recrystallizations from toluene yielded pure material; m. p. 113.5–115°, $[\alpha]^{23}D$ +19° (*c* 5.5, chloroform).

*Anal.* Calcd. for $C_{13}H_{18}O_{10}$: C, 46.71; H, 5.43; sapon. value (5 equivs.), 14.96 ml. 0.1 *N* NaOH per 100 mg. Found: C, 46.76; H, 5.26; sapon. value, 14.83 ml.

**Acknowledgment.**—One of us (A. T.) acknowledges fellowship fund support granted by The Ohio State University Research Foundation to the University for aid in fundamental research (Project 7670-107).

(22) R. C. Hockett, J. B. Ames and A. Scattergood, *Abstracts Papers Am. Chem. Soc.*, **109**, 2R (1946).

## Summary

1. A synthesis of perseulose (L-galaheptulose) from L-galactono-γ-lactone is described.

2. The following substances are also described: D,L-galactonamide; the tetraacetates of D-lyxonic acid, L-galactono-γ-lactone and D,L-galactono-γ-lactone; the O-pentaacetates of L-galactonamide, D,L-galactonamide, L-galactonic acid, L-galactonyl chloride and 1-diazo-1-desoxy-*keto*-L-galaheptulose; and the hexaacetate of *keto*-D,L-galaheptulose.

COLUMBUS, OHIO RECEIVED FEBRUARY 11, 1949

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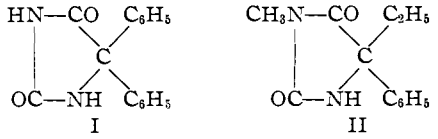
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

# Conversion of Alkyl 2-Anilino-2-phenylethyl Ketones into Hydantoins[1]

BY HENRY R. HENZE AND E. MURRAY WILLIAMS[2]

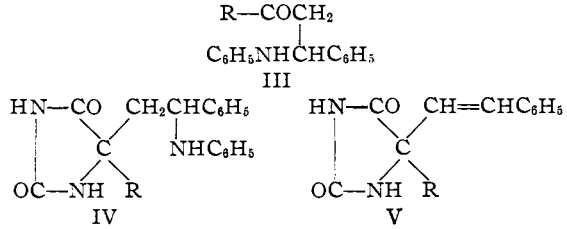
Although hydantoin is physiologically innocuous,[3] many of its derivatives have been shown to have activity as anticonvulsants[4] and two (I and II) are actually in general use in the control of epilepsy of the *grande mal* type. Disubstitution of



I II

alkyl or aryl groups at the 5-position of the hydantoin nucleus is likely to produce derivatives of limited solubility in water or acidic solutions, so it is really the more water-soluble sodium salt of 5,5-diphenylhydantoin (I) which is employed. However, in the case of a trisubstituted (3,5,5-) derivative, such as II, formation of a more soluble alkali-metal salt is impossible. Another approach to the problem of producing derivatives of more desirable solubility has been the incorporation, at the 5-position, of a grouping capable of yielding soluble salts with acids. For example, we have previously prepared hydantoins possessing 5-mono- or 5,5-disubstituted heterocyclic nitrogen groups.[5] Or the 5-alkyl or -aryl groupings have been further substituted with certain amino derivatives.

The availability of a series of anilino-substituted ketones (III), from reaction of benzalaniline with aliphatic ketones in the presence of boron trifluoride etherate,[6] suggested the possibility of their conversion into 5-alkyl-5-(2-anilino-2-phenylethyl) hydantoins through interaction with a cyanide and ammonium carbonate. The products of such reaction were found to be 5,5-disubstituted hydantoins, but not of the structure anticipated (IV).



III

IV V

(1) From the M.A. thesis of E. M. Williams, January, 1949.

(2) Present address: Tennessee Eastman Co., Kingsport, Tenn.

(3) Lewis, *J. Biol. Chem.*, **13**, 547 (1913).

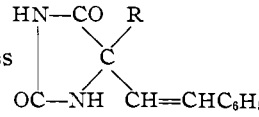
(4) Merritt, Tracy and Putnam, *Epilepsia*, 51 (1945).

(5) Unpublished results by Henze, *et al.*, include various pyridyl, quinolyl, isoquinolyl and polyaza products.

(6) Snyder, Kornberg and Romig, THIS JOURNAL, **61**, 3556 (1939)

TABLE I

5-ALKYL-5-STYRYLHYDANTOINS OBTAINED FROM ALKYL 2-ANILINO-2-PHENYLETHYL KETONES



| R | M. p., °C. | Yield, % | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| $-CH_3$ | 224–226[a] | 32 | 66.65 | 66.16 | 5.59 | 5.55 | 12.95 | 13.22 |
| $-CH_2CH_3$ | 210–211[b] | 37 | 67.82 | 67.57 | 6.12 | 6.13 | 12.16 | 12.45 |
| $-CH_2CH_2CH_3$ | 175–177[c] | 33 | 68.84 | 68.40 | 6.60 | 6.67 | 11.46 | 11.42 |
| $-CH(CH_3)_2$ | 220–221 | 35 | 68.84 | 68.06 | 6.60 | 6.79 | 11.46 | 11.55 |
| $-CH_2CH(CH_3)_2$[d] | 209–212 | 34[d] | 69.75 | 68.84 | 7.02 | 7.23 | 10.84 | 11.08 |
| $-CH_2CH(CH_3)_2$ | 169–172 | | 69.75 | 69.12 | 7.02 | 7.14 | 10.84 | 10.80 |

[a] Henze and Long, ref. 7, reported m. p. 222–223° (cor.). [b] *Idem.*, reported m. p. 211° (cor.). [c] *Idem.*, reported m. p. 171–174° (cor.). [d] The yield reported is that of partially purified material, repeatedly recrystallized from alcohol–water and from dioxane–water, melting reproducibly at 182–189°. Subsequent boiling with benzene yielded a sparingly soluble fraction of m. p. 209–212°, but recrystallized from alcohol–water, m. p. 209.0–210.5°; recrystallization of the portion more readily soluble in benzene, but insoluble in Skellysolve C, from alcohol–water yielded the fraction of m. p. 169–172°.

Determinations of the molecular weight of the products of reaction resulted in values definitely and consistently smaller than those expected. Moreover, the analytical data did not correspond to the calculated percentages, although the former were in satisfactory agreement for molecular formulas containing a lesser content of carbon and nitrogen. Examination of the reaction mixtures established the presence of aniline, which indicated that the hydantoins produced contained styryl, rather than β-anilino-β-phenylethyl, substitution.

Authentic samples were available for the first three members of a series of 5-alkyl-5-styrylhydantoins (V) produced several years ago in this Laboratory.[7] Comparisons between these authentic samples and the appropriate products of the present investigation established the identity of the latter. Further characterization of the ethyl, isopropyl and isobutyl members was obtained through catalytic hydrogenation to yield 5-alkyl-5-phenylethylhydantoins, of which the ethyl derivative[8] was available for comparison.

## Experimental

**Preparation of Alkyl 2-Anilino-2-phenylethyl Ketones.**—The methyl, ethyl, propyl and isobutyl analogs were resynthesized according to the procedure of Snyder, *et al.*,[6] and were further characterized by conversion into their 2,4-dinitrophenylhydrazones. The new isopropyl member was obtained in 61% yield; m. p. 117.5–119.0° (recrystallized from diluted alcohol); m. p. 115.5–117.0° (from dioxane–water).

*Anal.* Calcd. for $C_{18}H_{21}NO$: C, 80.91; H, 7.85; N, 5.24. Found: C, 80.71; H, 7.92; N, 5.24.

Subsequently to the attempt to convert these ketones into hydantoins, the propyl ketone was warmed with alcoholic potassium hydroxide solution; steam distillation of the reaction mixture yielded some aniline. Likewise, positive tests for aniline were found after warming at 60° for twenty-four hours a solution of this ketone in 70% ethyl alcohol solution with an equivalent amount of either potassium cyanide or ammonium carbonate.

**Conversion of Alkyl 2-Anilino-2-phenylethyl Ketones into Hydantoins.**—The preparations were accomplished by the Bucherer method[9] after the procedure of Henze and Long,[7] using fused acetamide, had been found to be unsatisfactory. In general, a ketone was dissolved in 4–6 times its own volume of ethyl alcohol, and, independently, potassium cyanide (2.5 equivalents) in an amount of water about one-fourth the volume used of alcohol. The two solutions were mixed and made homogeneous, if necessary, by addition of small amounts of alcohol or water, or both. Ammonium carbonate (4 equivalents) was added and the mixture was heated, in a flask provided with a condenser, at 60° for twenty-one hours and then at the reflux temperature for three hours.

The reaction mixture was filtered while hot, from any undissolved inorganic material. The filtrate was evaporated to about one-half volume by means of an air jet directed on its surface and was then acidified with dilute acid. After chilling, the precipitated material was removed by filtration and washed with water. The mother liquor was further concentrated as long as organic matter was obtainable.

The material thus obtained was partially purified by dissolving it in 10% sodium hydroxide solution, removing any unreacted ketone by extraction with ether, and reprecipitating the product by the addition of concentrated hydrochloric acid. Further purification was accomplished by recrystallizations from diluted alcohol or dioxane–water mixture.

The lack of solubility of the reaction product in acidic solution was behavior inconsistent for an anilino derivative. Molecular weight determinations, by the depression of the melting point of camphor or by elevation of the boiling point of acetone, yielded results 50–60 units smaller than calculated. Analyses of the products gave data (Table I) which did not check reasonably with those calculated for the anticipated products of type $C_nH_{(2n-17)}N_3O_2$. However, the data agreed quite well for compounds of type $C_nH_{(2n-12)}N_2O_2$; for such products the molecular weight data were in reasonable agreement.

The reaction products exhibited unsaturation to bromine; the amount utilized of the latter clearly represented one molar equivalent, rather than the three equivalents required by substitution in an anilino group. The identification of aniline in the reaction mixture strengthened the conviction that the reaction products were not anilino-substituted hydantoins. The belief that these unsaturated compounds might be styryl hydantoins was established by comparison with authentic samples previously prepared[7] of 5-methyl-, 5-ethyl- and 5-propyl-5-styrylhydantoins. Certain data for physical properties and from analyses of the reaction products are collected in Table I.

Further confirmation of the structure of the 5-ethyl member of the series was achieved through hydrogenation, in the presence of Adams platinum catalyst, to yield the known 5-ethyl-5-(2-phenylethyl)-hydantoin.[8] By the

(7) Henze and Long, THIS JOURNAL, **63**, 1941 (1941), reported synthesis of the methyl, ethyl, propyl and butyl styrylhydantoins.

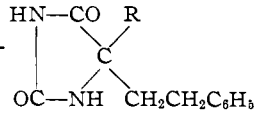
(8) Herbst and Johnson, *ibid.*, **54**, 2463 (1932).

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

same procedure, the 5-isopropyl and 5-isobutyl-5-styrylhydantoins were hydrogenated to the corresponding 5-(2-phenylethyl) derivatives. Certain data for these hydantoins are collected in Table II.

TABLE II

5-ALKYL-5-(2-PHENYLETHYL-HYDANTOINS



| R | M. p., °C. | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|
| $-CH_2CH_3$[a] | 196–198 | | | | |
| $-CH(CH_3)_2$ | 231–235 | 68.28 | 68.08 | 7.32 | 7.34 |
| $-CH_2CH(CH_3)_2$ | 177–181 | 69.21 | 68.31 | 7.69 | 7.42 |

[a] Herbst and Johnson, ref. 8, reported m. p. 198–199°.

## Summary

1 By interaction with potassium cyanide and ammonium carbonate, five-alkyl 2-anilino-2-phenylethyl ketones were converted into 5-alkyl-5-styrylhydantoins with elimination of aniline.

2. Two new 5-branched alkyl-5-phenylethylhydantoins have been prepared by catalytic hydrogenation of the corresponding styryl compounds.

AUSTIN, TEXAS RECEIVED FEBRUARY 4, 1949

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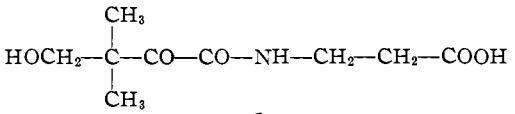
[FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

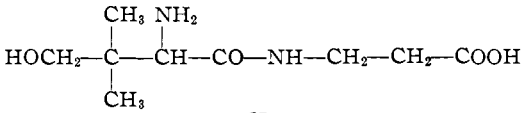
# Synthesis of Compounds Related to Pantothenic Acid[1]

BY S. H. LIPTON[2] AND F. M. STRONG

Among the numerous structural analogs of pantothenic acid which have been described, only a few possess appreciable vitamin activity (hydroxypantothenic acid,[3] pantothenol[4]), while several others are metabolic inhibitors of pantothenic acid (pantoyltaurine[5,6,7] phenylpantothenone[8]). In view of known biochemical interrelationships between structurally similar hydroxy, keto and amino compounds, it seemed of interest to study the biological properties of the keto (I) and amino (II) analogs of pantothenic acid.



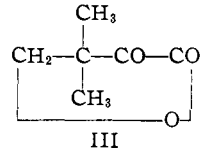
I



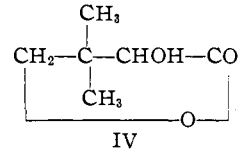
II

Efforts to prepare the keto analog (I) are described in the present paper.[9]

The proposed synthesis of the keto analog (I) involved condensation of β-alanine with the corresponding keto lactone (III), or derivatives thereof.



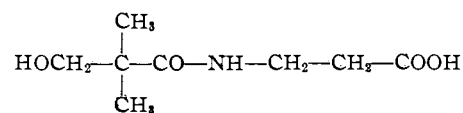
III



IV

Since the keto lactone (III) prepared from dimethylpyruvic acid and formaldehyde according to the method of Kuhn and Wieland[10] melted appreciably higher than their product and considerable difficulty was encountered in attempting to condense it with β-alanine, some doubt arose as to its identity. Therefore, it was also prepared by an alternative method, namely, the oxidation of *d,l*-pantolactone (IV) by lead tetraacetate. The two products were identical, and on reduction consumed one mole of hydrogen with the formation of *d,l*-pantolactone (IV) which yielded microbiologically active[11] *d,l*-pantothenic acid when condensed with β-alanine.

Condensation of the keto lactone (III) with β-alanine gave mixtures from which no "ketopantothenic" acid (I) could be isolated, although catalytic reduction of the crude products followed by microbiological estimation of pantothenic acid activity indicated that 13–15% of the keto analog was formed under certain conditions. However, two other nitrogenous, acidic compounds were obtained from this condensation. Analysis indicated one of these corresponded to I minus a molecule of carbon monoxide, and since in addition it had no carbonyl function, it was formulated as N-(α,α-dimethyl-β-hydroxypropionyl)-β-alanine (V).



V

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Committee.

(2) From the Ph.D. dissertation of S. H. Lipton, 1948; present address: Department of Obstetrics and Gyuecology, University of Chicago.

(3) Mitchell, Snell and Williams, THIS JOURNAL, **62**, 1791 (1940).

(4) Pfaltz, *Z. Vitaminforsch.*, **13**, 236 (1943).

(5) Snell, *J. Biol. Chem.*, **139**, 975 (1941); **141**, 121 (1941).

(6) Barnett and Robinson, *Biochem. J.*, **36**, 357, 364 (1942).

(7) Kuhn, Wieland and Moeller, *Ber.*, **74**, 1605 (1941).

(8) Woolley and Collyer, *J. Biol. Chem.*, **159**, 263 (1945).

(9) The synthesis and biological inactivity of the amino analog (II) have very recently been reported by Folkers, *et al.*, THIS JOURNAL, **70**, 3088 (1948).

(10) Kuhn and Wieland, *Ber.*, **75**, 121 (1942).

(11) Dann and Satterfield, *Biol. Symposia*, **12**, 273 (1947).