Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.0; H, 4.6. Found: C, 51.7; H, 4.9.

In ether solution this neutral product was not hydrolyzed with sodium bicarbonate solution but when it was digested with a dilute solution of hydrochloric acid in acetic acid it regenerated the higher-melting hydroxy ketonic acid.

In solutions of acetic anhydride and acetic acid both hydroxy acids failed to react at the ordinary temperature. With heating in such solutions both hydroxy acids gave oils which invariably gave both the hydroxy acids on standing or when their ether solutions were extracted with dilute sodium bicarbonate. On the basis of the experiments with acetic anhydride only the higher-melting acid forms a dicyclic acetate and in this acid the carboxyl and bromobenzoyl groups are on the same side of the ring as shown in formula XV.

Summary

The configurations of two cyclic diastereomeric β-bromo γ-keto acids have been established. The bromo acid in which the bromine and carboxyl groups are in the *cis* position is the only one that will form a β-lactone. Evidence is given to show that this β-lactone formation has occurred without inversion. The β-lactone is opened with bases to give a single hydroxy acid. The evidence indicates that this hydroxy acid has the same configuration as the β-lactone and the bromo acid from which it is prepared.

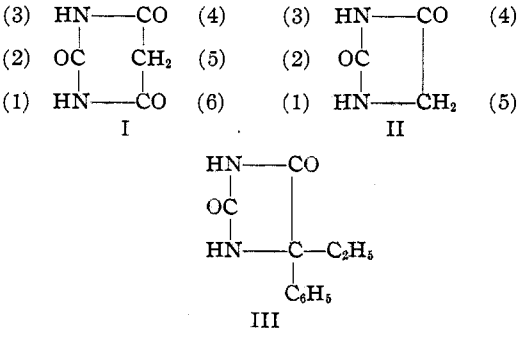
CAMBRIDGE, MASS. RECEIVED JUNE 27, 1938

[CONTRIBUTION NO. 135 FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

5,5-Dialkylhydantoins Containing a Dialkylamino Substituent[1,2]

BY J. WM. MAGEE WITH HENRY R. HENZE

Attempts to relate chemical constitution to physiological activity have been of but moderate success and the information thus secured has been used in the development of the barbituric acid series of soporifics.[3,4] Synthesis of additional derivatives in this field has continued with the production of only a few new types. More recently interest has again been centered in the preparation of sedatives through the replacement of the hydrogen attached to the nitrogen of the barbituric acid nucleus by alkyl groups.[5,6] Here, particularly, the substitution of the methyl group for the imidic hydrogen has in certain instances produced compounds of extremely short but intense period of hypnotic activity.[7] A late publication includes evidence of success in the introduction of alkylamino groupings[8] into the alkyl commonly attached to the 5-position of the heterocycle.



A definite similarity exists in the structure of barbituric acid (I) and hydantoin (II), and rather close analogy is evident in the fact of the existence of compounds derived from substitution of identical groupings for the hydrogen atoms in the 5,5-, 1- and 3-positions of both the barbituric acid and hydantoin heterocycles.[4,6,9-11] Although, as yet, but one 5,5-disubstituted hydantoin[12] (III) has found clinical use, the hydantoin nucleus is innocuous and offers hope that additional compounds of value as sedatives may be derived from it by appropriate substitution. In this Laboratory attention has previously been directed to the utilization of alkoxyalkyl[13] and aryloxyalkyl[14] substituents and compounds of definite hypnotic power but unfavorable toxicity have been pro-

(1) From a portion of a dissertation presented by J. Wm. Magee to the Faculty of the Graduate School of The University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1938.

(2) Presented before the Division of Medicinal Chemistry at the 95th meeting of the American Chemical Society, Dallas, Texas, April 18 to 21, 1938.

(3) Shonle, *Ind. Eng. Chem.*, **23**, 1104 (1931).

(4) Shonle, Waldo, Keltch and Coles, THIS JOURNAL, **58**, 585 (1936).

(5) U. S. Patent 1,073,380 (Sept. 16, 1913); U. S. Patent 1,074,030 (Sept. 30, 1913); German Patent 537,366 (July 9, 1929); British Patent 401,693 (Nov. 17, 1933); U. S. Patent 1,947,944 (Feb. 20, 1934); German Patent 606,499 (Dec. 4, 1934).

(6) Dox and Jones, THIS JOURNAL, **51**, 316 (1929); Shonle and Doran, *ibid.*, **58**, 1358 (1936); Buck, Hjort, Ide and DeBeer, *ibid.*, **60** 461 (1938).

(7) Tabern and Volwiler, *ibid.*, **58**, 1354 (1936).

(8) Rosenberg, Kneeland and Skinner, *ibid.*, **56**, 1339 (1934).

(9) Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

(10) Bucherer and Lieb, *J. prakt. Chem.*, **141**, 5 (1934).

(11) Biltz and Slotta, *ibid.*, **113**, 245, 255 (1926).

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

(13) Rigler with Henze, THIS JOURNAL, **58**, 474 (1936).

(14) Whitney with Henze, *ibid.*, **60**, 1148 (1938).

duced.[13] These hydantoin derivatives have been obtained from alkoxy- and aryloxy-dialkyl ketones and from alkoxyalkyl aryl ketones by adaptation of Bucherer's method[15] for synthesizing simple hydantoins. This process is much simpler and productive of better yields than is that of Bergs.[16]

The purpose of the present investigation was to obtain 5,5-dialkylhydantoins containing dialkylamino substituents. Although 1-alkyl-5,5-dialkylhydantoins[11] have been prepared, a thorough search of the literature fails to disclose the synthesis of 5-dialkylaminoalkyl-5-alkylhydantoins. In fact, Slotta, Behnisch, and Szyszka[17] reported that they were unable to convert dimethylaminoacetone and *bis*-dimethylaminomethyl ketone into the corresponding hydantoins by means of Bergs' procedure.[16] The former of these ketones, as well as nine other disubstituted aminoacetones, have been prepared in this research and all subsequently converted into 5-dialkyl- or diallyl-aminomethyl-5-methylhydantoins by adaptation of the method of Bucherer.[15]

Five of the dialkylaminoacetones had been synthesized previously but inadequately characterized. Marked discrepancies were found between the melting points of the semicarbazones of three of these ketones as recorded in the literature[18] and as determined in the course of this study.

Experimental

Bromoacetone.—The bromoacetone was prepared by slightly altering Levene's[19] modification of Nef's[20] method. It seemed advantageous to decrease by one-third the volume of water used and to heat on a steam-cone. Using an efficient mechanical stirrer, it was possible to add the required amount of bromine rapidly through a short separatory funnel. Experimental runs using 10 moles of acetone produced 800 g. of bromoacetone in about 55% of the theoretical yield and in sufficient state of purity to use without redistillation.

Preparation of the Disubstituted Aminoacetones.—Two general procedures were used for preparing the dialkylaminoacetones. In one method two moles of a specific secondary aliphatic amine, diluted with 20 volumes of ether, was treated with one mole of bromoacetone diluted with 2 volumes of ether. Usually the hydrobromide of the secondary amine separated as glistening, white leaflets from the reddish-brown colored solution. The ether solution was refluxed until the odor of bromoacetone was no longer evident, chilled in an ice-bath and filtered. The filtrate was fractionated under diminished pressure. In order to avoid the conversion of one-half of the secondary amine into the hydrobromide salt, a second method was developed. To one mole of the secondary amine, suspended in 5 volumes of water containing 2 moles of sodium carbonate, was added one mole of bromoacetone with vigorous stirring during thirty minutes or until the odor of bromoacetone could not be recognized. After filtration from the sodium bicarbonate formed, the filtrate was extracted with ether and the extract dried over anhydrous sodium sulfate before fractionation. Only in the cases of the di-*s*-propyl and di-*s*-butyl compounds was this second method unsuccessful. In these two instances the rate of reaction between the secondary amine and the bromoacetone seemed slower than the rate of decomposition of the bromoacetone by the alkali.

Although the di-*s*-butylaminoacetone was refractionated a number of times, and the analytical results seemed to indicate a state of satisfactory purity, the observed molecular refractivity and parachor did not check the calculated values very closely. Hence the liquid was treated with enough 6 *N* hydrochloric acid to dissolve 90–95% of the material; the acid solution was extracted with ether and then neutralized with sodium hydroxide. The regenerated amino ketone was treated with such a quantity of 6 *N* acid as to dissolve only 5–10% of the material. The residual liquid was washed free of any salt, dried and distilled. The physical properties of the fractionated material were not appreciably altered by this treatment.

All the ketones included in this study are colorless oils when freshly and carefully fractionated, possess a strong basic odor, but darken after standing even for a short time. Only one of the ketones, dimethylaminoacetone, is readily miscible with water but all are soluble in the usual organic solvents such as ether, acetone, alcohol, benzene, and chloroform. The amino ketones are readily dissolved by acids, as hydrochloric, sulfuric, and acetic.

Boiling points were taken with calibrated thermometers and the properly corrected values are reported for the disubstituted aminoacetones. Surface tensions were measured by means of Cassel's[21] precision capillarimeter at 20°. Densities were determined by means of a U-shaped glass tube weighing 1.7231 g. and containing 1.1384 cc. of water at 4°. The data resulting from the determination of physical constants, the values derived from these data by calculation and such information as was obtained through analysis of the substituted aminoacetones have been tabulated in Table I.

Preparation of Semicarbazones from Disubstituted Aminoacetones.—Solid, crystalline semicarbazones were obtained from all of the disubstituted aminoacetones. Those derived from dimethyl- and diethylaminoacetones, whose syntheses have not been reported previously, were so soluble in water as to present difficulty in their isolation. They were obtained best by making a

(15) Bucherer and Fischbeck, *J. prakt. Chem.*, [2] **140**, 69 (1934); Bucherer and Brandt, *ibid.*, 129; Bucherer and Barsch, *ibid.*, 151; Bucherer and Steiner, *ibid.*, 291; Bucherer and Lieb, *ibid.*, **141**, 5 (1934).

(16) German Patent 566,094 (Dec. 1, 1932).

(17) Slotta, Behnisch and Szyszka, *Ber.*, **67B**, 1529 (1934).

(18) Stoermer and Pogge, *ibid.*, **29**, 866 (1896).

(19) Levene, "Organic Syntheses," John Wiley & Sons, Inc., New York, N. Y., Vol. X, 1930, pp. 12–13,

(20) Nef, *Ann.*, **335**, 259 (1904).

(21) Cassel, *Chem. Ztg.*, **53**, 479 (1929).

TABLE I

DISUBSTITUTED AMINOACETONES, $R_2NCH_2COCH_3$

	−R	B. p., °C. (corr.)	Mm.	Density d^{23}_4	Ref. index $n^{20}D$	Surface tension γ 20 dynes/cm.	Free surface energy $\gamma(m/d)^{2/3}$	Yield, %
1	$-CH_3$	31.6[a]	27	0.8688	1.4131	27.77	662.1	36
2	$-CH_2CH_3$	69.6[a]	32	.8620	1.4249	26.67	752.5	48
3	$-CH_2CH_2CH_3$	64.6[b]	8	.8520	1.4297	26.69	853.3	72
4	$-CH(CH_3)_2$	79.7	17	.8593	1.4324	27.37	882.1	69
5	$-CH_2CH_2CH_2CH_3$	86.7	3	.8505	1.4359	27.20	985.1	71
6	$-CH_2CH(CH_3)_2$	80.7[b]	9	.8426	1.4315	28.34	1032.5	58
7	$-CH_2CH(CH_3)CH_3$	104.7	14	.8749	1.4422	28.70	1020.0	64
8	$-CH_2CH_2CH_2CH_2CH_3$	110.2	7	.8411	1.4382	27.49	1163.7	69
9	$-CH_2CH_2CH(CH_3)_2$	78.7[b]	2	.8436	1.4379	26.55	1121.3	56
10	$-CH_2CH{:}CH_2$	80.7	22	.8890	1.4586	28.59	885.5	70

[a] Stoermer and Dzimski, *Ber.*, **28**, 2223 (1895), reported only the following boiling points for these ketones: dimethylaminoacetone, 123°; diethylaminoacetone, 155–156° with some decomposition.

[b] Stoermer and Pogge[18] reported for certain of these dialkylaminoacetones the following data which are noticeably at variance with the data included in Table I.

	B. p., °C.	d 17°
Di-*n*-propylaminoacetone	188	0.8337
Diisobutylaminoacetone	206–207	.8735
Diisoamylaminoacetone	219–220	.8911

R	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Mol. ref. Calcd.	Found	ΔMR	Parachor Calcd.	Found	ΔP
1	59.37	59.18	10.96	10.95	29.24	29.04	−0.20	267.8	265.7	− 2.1
2	65.07	65.02	11.70	11.82	38.48	38.34	− .14	345.8	340.6	− 5.2
3	68.74	68.30	12.18	12.24	47.71	47.64	− .07	423.8	419.5	− 4.3
4	68.74	68.48	12.18	12.25	47.71	47.52	− .19	423.8	418.6	− 5.2
5	71.29	71.18	12.51	12.43	56.95	56.98	+ .03	501.8	497.6	− 4.2
6	71.29	71.16	12.51	12.51	56.95	56.98	+ .03	501.8	507.4	+ 5.6
7	71.29	71.21	12.51	12.37	56.95	56.06	− .89	501.8	490.2	−11.6
8	73.18	73.16	12.76	13.06	66.19	66.46	+ .27	579.8	579.5	− 0.3
9	73.18	73.14	12.76	12.95	66.19	66.29	+ .10	579.8	573.6	− 6.2
10	70.54	70.38	9.87	9.65	46.78	47.10	+ .22	400.8	398.6	− 2.2

concentrated solution of semicarbazide hydrochloride in the amino ketone, adding a slight excess of dilute aqueous solution of sodium hydroxide, and chilling in an ice-bath. Recrystallization of all semicarbazones is accomplished readily by solution in hot benzene and precipitation from the cooled solution by addition of several volumes of petroleum ether. The corrected melting points of, and the analytical constants for, the ten semicarbazones are collected in Table II. It is to be noted that the melting points of three of these semicarbazones, namely, of the di-*n*-propyl, diisobutyl and diisoamyl derivatives differ, as do the densities of the respective amino ketones, from those reported by Stoermer and Pogge.[18] In view of these discrepancies all three of the dialkylaminoacetones were resynthesized and their semicarbazones prepared again and carefully purified and dried. The melting points and analytical data checked closely those of the first preparations.

TABLE II

SEMICARBAZONES OF DISUBSTITUTED AMINOACETONES

$$R_2NCH_2C(CH_3)=NNHCONH_2$$

	−R	M. p. °C. (corr.)	Nitrogen, % Calcd.	Found
1	$-CH_3$	137	35.42	35.27
2	$-CH_2CH_3$	143	30.41	30.55
3	$-CH_2CH_2CH_3$	150[a]	26.14	26.13
4	$-CH(CH_3)_2$	195	26.14	25.94
5	$-CH_2CH_2CH_2CH_3$	132	23.12	23.38
6	$-CH_2CH(CH_3)_2$	175[a]	23.12	23.13
7	$-CH_2CH(CH_3)CH_3$	196	23.12	23.10
8	$-CH_2CH_2CH_2CH_2CH_3$	102	20.72	20.62
9	$-CH_2CH_2CH(CH_3)_2$	124[a]	20.72	20.82
10	$-CH_2CH{=}CH_2$	105	26.64	26.73

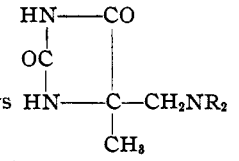
[a] Stoermer and Pogge [*Ber.*, **29**, 866 (1896)] report the following melting points:

	−R	M. p., °C.
3	$-CH_2CH_2CH_3$	110
6	$-CH_2CH(CH_3)_2$	132
9	$-CH_2CH_2CH(CH_3)_2$	166

Formation of the Disubstituted Aminohydantoins.—The hydantoins were easily synthesized directly from the substituted aminoacetones by subjecting the carbonyl compounds to the action

TABLE III

DISUBSTITUTED AMINOHYDANTOINS



	−R	Yield, %	M. p., °C. (corr.)	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	$-CH_3$	32	177	24.55	24.64	49.11	49.14	7.65	7.67
2	$-CH_2CH_3$	38	196	21.09	21.32	54.25	54.02	8.60	8.61
3	$-CH_2CH_2CH_3$	84	161	18.49	18.72	58.12	58.23	9.31	9.14
4	$-CH(CH_3)_2$	77	198	18.49	18.31	58.12	58.26	9.31	9.23
5	$-CH_2CH_2CH_2CH_3$	73	173	16.46	16.76	61.14	61.30	9.87	10.03
6	$-CH_2CH(CH_3)_2$	62	222	16.46	16.50	61.14	61.24	9.87	9.79
7	$-CH_2CH(CH_3)CH_3$	68	233	16.46	16.60	61.14	61.20	9.87	9.77
8	$-CH_2CH_2CH_2CH_2CH_3$	92	171	14.83	15.04	63.57	63.74	10.29	10.29
9	$-CH_2CH_2CH(CH_3)_2$	98	204	14.83	14.97	63.57	63.85	10.29	10.39
10	$-CH_2CH{=}CH_2$	91	135	18.82	18.71	59.17	59.50	7.68	7.59

of potassium cyanide and ammonium carbonate in alcoholic solution according to directions of Bucherer.[15] To an Erlenmeyer flask fitted with an air condenser were added 0.10 mole of ketone, 0.30 mole of freshly powdered ammonium carbonate, 0.13 mole of potassium cyanide, and 7–8 volumes of 50% alcohol,[22] and the mixture heated for about eight hours. As the carbonate and cyanide gradually dissolved, gas was evolved and ammonium carbonate formed in the condenser tube. Near the end of the period of heating the condenser tube was removed and the temperature of the bath increased to evaporate the alcohol. Cooling in an ice–salt mixture caused most of the hydantoin to separate and only an additional, small amount was obtained when the solution was neutralized with dilute hydrochloric acid. Because of the dialkylamino substituent, all of the hydantoins are soluble in acid so an excess of the latter was avoided.

The hydantoins are easily recrystallized from dilute alcohol, are soluble in the ordinary organic solvents and, with the exception of the dimethyl homolog, very sparingly soluble in water. Because the compounds are amphoteric they are soluble in both acidic and alkaline solutions from which they are readily precipitated unchanged when such solutions are made exactly neutral. The disubstituted aminohydantoins are stable, white, crystalline solids which melt without decomposition to clear straw colored liquids. The temperatures reported as melting points of the hydantoins in Table III represent corrected values.

(22) Due to the solubility of the dimethylaminoacetone no alcohol was used in the preparation of 5-dimethylaminomethyl-5-methylhydantoin.

Summary

1. The series of 5,5-dialkylhydantoins has been extended by the synthesis of nine examples of dialkylamino derivatives. Likewise the production of 5-diallylaminomethyl-5-methylhydantoin represents the initial preparation of an additional type.

2. Although Slotta, Behnisch and Szyszka were unable to convert dimethylaminoacetone into 5-dimethylaminomethyl-5-methylhydantoin by means of the method of Bergs, this conversion has now been accomplished utilizing the closely related method of Bucherer.

3. Diallylaminoacetone and four new members of the series of dialkylaminoacetones have been prepared and five additional examples of this type have been resynthesized and all adequately characterized. The densities of three of the ketones are in definite disagreement with the data previously reported in the literature.

4. The yield of disubstituted aminoacetones, as based on the weight of the secondary amine used, has been doubled by using dilute alkali to prevent the formation of the secondary amine hydrobromide.

5. Semicarbazones, useful in the identification of the amino ketones, were obtained from each of the ten members of this series. The melting points of the semicarbazones of three of the disubstituted aminoacetones are quite different from those reported in a prior investigation.

6. For diallylaminoacetone and the series of dialkylaminoacetones studied in this investigation, the molecular refraction was found to be more sensitive than the parachor as an index to purity.

AUSTIN, TEXAS RECEIVED JUNE 13, 1938