

be expected on the basis of the melting points of the other members of the series. Certain data concerning these ten new hydantoin are listed in Table II.

Summary

Using fused acetamide as a solvent, our modification of the Bucherer process has been employed

in the synthesis of twenty-one new hydantoin. Eleven of these contain a biphenyl grouping attached to the hydantoin nucleus; ten are of the bis-hydantoin type in which two hydantoin nuclei are joined through the biphenyl group.

AUSTIN, TEXAS

RECEIVED APRIL 29, 1941

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

Synthesis of 5-Disubstituted Aminomethyl-5-phenethylhydantoin¹

By HENRY R. HENZE AND CHARLES B. HOLDER²

The preparation of a series of 5-disubstituted aminomethyl-5-methylhydantoin from disubstituted aminoacetones, $\text{CH}_3\text{COCH}_2\text{NR}_2$, has been reported recently.³ However, there is ample reason to anticipate that derivatives of dimethylhydantoin would have less physiological activity than those disubstituted hydantoin in which each substituent is a higher alkyl or a phenyl group. Likewise certain unpublished work in this Laboratory has indicated that the phenethyl group has but little hypnotic activity but considerable anticonvulsant value. Therefore the present investigation involved the preparation of related hydantoin in which one substituent should be the phenethyl group. Synthesis of the desired hydantoin from appropriate phenethyl ketones could be anticipated by utilization of Bucherer's⁴ method.

Production of seven disubstituted aminomethyl phenethyl ketones, $\text{R}_2\text{NCH}_2\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5$, was effected by interaction of appropriate secondary amines and 1-chloro-4-phenylbutanone-2⁵ following the procedure developed in this Laboratory.³ Although this chloro ketone⁵ had been prepared from diazomethane and hydrocinnamoyl chloride, we preferred to attempt its synthesis by oxidation of the corresponding secondary alcohol, namely, 1-chloro-4-phenylbutanol-2, which was available through interaction of epichlorohydrin and benzylmagnesium chloride.^{6,7} Although the yield realized from the Grignard reaction is less than that reported using diazomethane, utiliza-

tion of a poisonous and explosive substance was avoided.

1-Chloro-4-phenylbutanone-2 was utilized in the preparation of the six new disubstituted aminomethyl phenethyl ketones listed in Table I. By interaction of each of these amino ketones with potassium cyanide and ammonium carbonate, the corresponding 5-disubstituted aminomethyl-5-phenethylhydantoin were obtained. This represents the initial synthesis of these six compounds, as well as of 5-(N-ethyl-N-phenylaminomethyl)-5-phenethylhydantoin, the latter being prepared from an only partially purified sample of the corresponding ketone. Certain data for these seven hydantoin are listed in Table II.

Experimental

1-Chloro-4-phenylbutanol-2.—The preparation of this compound was accomplished through the method described by Koelsch and McElvain.⁷ The chlorohydrin was obtained initially as a liquid; b. p. 112–114° (4 mm.), n_D^{20} 1.5378, d_4^{20} 1.1282, M_R calcd. 51.17, M_R found 51.18. However, the product solidified; yield 45% of the theoretical; after three recrystallizations from petroleum ether, m. p. 46–47° (cor.).

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{ClO}$: C, 65.04; H, 7.10; Cl, 19.20. Found: C, 64.90; H, 7.10; Cl, 19.15.

1-Chloro-4-phenylbutanone-2.—This chloro ketone was prepared by the chromic acid oxidation⁸ of 1-chloro-4-phenylbutanol-2. From 194.5 g. of the latter, there was obtained 157.5 g. (82% yield) of solid melting at 35–40°; after recrystallization from alcohol-water and from petroleum ether, m. p. 40–41° (cor.). The melting point was lowered only about 1.5° by fusion, continued heating to 120°, solidification and refusion.

Since Clibbens and Nierenstein⁵ had reported a melting point of 84–85° for this compound, the apparently pure chloro ketone was distilled under diminished pressure and

(1) Presented before the Division of Organic Chemistry at the 101st meeting of the American Chemical Society at St. Louis, Missouri, April 8–10, 1941.

(2) From the Ph.D. dissertation of C. B. Holder, June, 1941.

(3) Magee and Henze, *THIS JOURNAL*, **60**, 2148 (1938).

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

(5) Clibbens and Nierenstein, *J. Chem. Soc.*, **107**, 1493 (1915).

(6) Fournneau and Tiffeneau, *Bull. soc. chim.*, [4] **1**, 1231 (1907).

(7) Koelsch and McElvain, *THIS JOURNAL*, **52**, 1164 (1930).

(8) We adopted the directions for the preparation of *sym*-dichloroacetone [*"Organic Syntheses,"* John Wiley and Sons, Inc., New York, Collective Volume I, 1932, page 206] except that 50% acetone-water solution served as solvent.

TABLE I

PHYSICAL PROPERTIES AND ANALYTICAL DATA FOR THE DISUBSTITUTED AMINOMETHYL PHENETHYL KETONES PREPARED IN THIS INVESTIGATION: $RCH_2COCH_2CH_2C_6H_5$

R	B. p. °C. (cor.)	Mm.	Yield, %	n_D^{20}	d_4^{20}	Mol. refract.		Carbon, %		Hydrogen, %		Nitrogen, %	
						Obsd.	Σ	Calcd.	Found	Calcd.	Found	Calcd.	Found
$(CH_3)_2N-$	106-107	3.5	35.43	1.5070	0.9822	57.96	57.97	75.35	75.09	8.96	9.04	7.32	7.35
$(C_2H_5)_2N-$	119	4	58	1.5030	.9669	67.05	67.20	76.66	76.26	9.65	9.59
$(n-C_3H_7)_2N-$	136-138	4	55	1.4959	.9447	76.48	76.44	77.68	77.44	10.19	10.16	5.66	5.61
$(n-C_4H_9)_2N-$	159-160	5.5	36.47	1.4927	.9329	85.75	85.67	78.49	78.30	10.61	10.52	5.09	5.10
$(i-C_4H_9)_2N-$	161-163	4	33	1.4900	.9259	94.78	94.91	79.15	78.72	10.96	10.83	4.62	4.42
$O(CH_2CH_2)_2N-$	180-181	7	81	1.5260	1.0760	66.58	66.74	72.07	71.80	8.21	8.23	6.00	5.76

TABLE II

PICRATES OF THE DISUBSTITUTED AMINOMETHYL PHENETHYL KETONES PREPARED IN THIS INVESTIGATION

Amino substituent	M. p., °C. (cor.)	Carbon, %		Hydrogen, %		Nitrogen, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
$(CH_3)_2N-$	118.0-119.0	51.43	51.45	4.80	4.90	13.33	13.13
$(C_2H_5)_2N-$	104.5-105.5	53.57	53.70	5.39	5.45	12.50	12.21
$(n-C_3H_7)_2N-$	116.5-117.5	55.45	55.36	5.92	5.97	11.76	11.61
$(n-C_4H_9)_2N-$	99.0-100.0	57.13	57.25	6.39	6.45	11.11	11.04
$(i-C_4H_9)_2N-$	Oil
$O(CH_2CH_2)_2N-$	136.3-137.3	51.95	51.71	4.80	4.90	12.12	11.88

TABLE III

5-DISUBSTITUTED AMINOMETHYL-5-PHENETHYLHYDANTOINS
PREPARED IN THIS INVESTIGATION

R	M. p., °C. (cor.)	Yield, %	Carbon, %		Hydrogen, %		Nitrogen, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
$(CH_3)_2N-$	232.3-233.3	62	64.34	64.43	7.33	7.39	16.08	16.11
$(C_2H_5)_2N-$	203.3-205.3	91.5	66.41	66.36	8.01	8.15	14.52	14.39
$(n-C_3H_7)_2N-$	196.5-197.5	93	68.10	68.36	8.57	8.56	13.24	13.09
$(n-C_4H_9)_2N-$	161.0-163.0	70.6	69.54	69.38	9.05	9.02	12.17	12.16
$(i-C_4H_9)_2N-$	124.7-127.2	73	70.74	70.57	9.44	9.58	11.25	11.26
$O(CH_2CH_2)_2N-$	222.0-223.0	97	63.34	63.36	6.98	7.10	13.85	13.76
$(C_2H_5)(C_6H_5)N-$	176.0-177.5	25 ^a	71.19	71.11	6.87	7.01	12.45	12.15

^a Based on an impure ketone.

collected in three fractions, each boiling at 110.5-111.5° (cor.) (5 mm.), n_D^{20} 1.5240, d_4^{20} 1.1224, M_R calcd. 49.66, M_R found 49.78. All three fractions solidified and melting points were 40-41°.

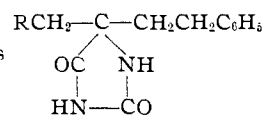
Anal. Calcd. for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.41. Found: C, 65.58; H, 6.12; Cl, 19.45.

The 2,4-dinitrophenylhydrazone was prepared in 90% yield. After recrystallization from alcohol and from ethyl acetate, m. p. 147.2-147.7° (cor.).

Anal. Calcd. for $C_{16}H_{15}ClN_4O_4$: Cl, 9.77; N, 15.45. Found: Cl, 9.68; N, 15.23.

The Disubstituted Aminomethyl Phenyl Ketones.—

Excepting the dimethylamino member, these ketones were prepared by interaction of 1-chloro-4-phenylbutanone-2 with slightly more than two equivalents of the appropriate secondary amine in ether or benzene solution in an ice-bath. The bath was allowed to come to room temperature and the mixture stood for two to three days until separation of the secondary amine hydrochloride had become complete. After filtration, the filtrate was washed with water and then extracted with dilute hydrochloric acid. The acidic extract was made definitely alkaline, extracted with ether and the latter dried over anhydrous sodium sulfate before fractionation. To prepare the simplest member of the series, the chloro ketone was dissolved



in acetone and added to a chilled mixture of acetone-water, dimethylamine hydrochloride and (anhydrous) sodium carbonate.³ After standing four days, the suspended inorganic salts were filtered and the amino ketone recovered in the usual manner.

The amino ketones thus prepared are liquids (the morpholino compound solidified in the refrigerator and melts at 23-24°) of pale-yellow tint with characteristic odor. Even when quite pure, with the exception of the liquid morpholino derivative, the amino ketones darken in color slowly on standing. The physical properties and analytical data for these ketones are listed in Table I.

To aid in characterization, solid, crystalline picrates were obtained from the ketoamines described herein, excepting the diisomyl member, the amine being suspended in water, dissolved with the aid of sulfur dioxide, and precipitated by addition of a saturated aqueous solution of picric acid. The dimethyl and di-*n*-butyl amino ketones formed sparingly soluble bisulfite compounds, hence alcoholic solutions of ketoamine and of picric acid were used to form these two picrates. Data for melting points and analyses of the picrates are listed in Table II.

5-Disubstituted Aminomethyl-5-phenethylhydantoin.—Each amino ketone was placed in solution in 50-65% alcohol with 1.3 equivalents of potassium cyanide and 3.3

equivalents of ammonium carbonate (cubes) and the mixtures were heated at 58–60° for ten to twenty hours. In most cases, part of the hydantoin separated as a white, almost pure solid from the warm solution and chilling caused practically all of the hydantoin to crystallize from the reaction solution. The hydantoin was recrystallized from alcohol–water or acetone–water; in general, the melting point of the crude material was not raised as much as 2° by repeated recrystallization.

Although these new hydantoin are amphoteric, their basic properties are more pronounced than are the acidic. Certain pertinent data for the hydantoin have been collected in Table III.

Summary

1. There have been re-synthesized 1-chloro-4-phenylbutanol-2 and 1-chloro-4-phenylbutanone-2; certain physical properties determined for these compounds are not entirely in agreement with those previously reported in the literature.

2. Six new disubstituted amino ketones have been prepared.

3. Seven new disubstituted aminomethyl-phenethylhydantoin have been obtained.

AUSTIN, TEXAS

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

1-Alkyl 2-Dialkylaminoalkyl 3-Aminophthalates as Local Anesthetics

BY F. F. Blicke and Chieko Otsuki¹

Many years ago Pyman^{2a} stated that the hydrochloride of the bis-(β -diethylaminoethyl) ester of phthalic acid (I) lacks local anesthetic properties. However, methyl β -diethylaminoethyl phthalate (II) has been described in a German patent^{2b} as a very good local anesthetic.

It seemed to us that more satisfactory products would be obtained if a nuclear amino group were introduced into esters of type II, consequently, we prepared a series of 1-alkyl 2-dialkylaminoalkyl 3-aminophthalates (III).

Our expectation that these esters would be found to be strong anesthetics proved to be correct. In fact, many of them were shown to be more potent than cocaine when tested on the rabbit cornea. Especially active are the 1-*n*-butyl, 1-*n*-amyl and 1-*n*-hexyl 2-diethylaminoethyl 3-aminophthalates.

The esters were tested by L. W. Rowe in the Parke, Davis and Company Laboratories. A detailed pharmacological report will be published by him in another journal.

Three different methods (A, B and C), illustrated in the case of 1-ethyl 2-(β -diethylaminoethyl) 3-aminophthalate, were employed for the preparation of the diesters.

The monoesters V, IX and XI were synthesized by interaction of 3-nitrophthalic acid with the required alcohol and sulfuric acid (V), and from

reaction of 3-nitrophthalic anhydride with a dialkylaminoalkanol (IX) or with ethylene bromohydrin (XI).

In order to obtain the diesters, a compound of type V was heated with a dialkylaminoalkyl chloride whereupon an ester of type VI was formed in good yield. This latter procedure is one which Horenstein and Pählicke³ used originally for the preparation of dialkylaminoalkyl esters of hydroxy acids. The diesters (VI and XIII) were obtained also from the monoesters IX and XI by treatment of the ester-acid chlorides (X and XII) with an alcohol.

Reduction of the nitro diester to the corresponding amino compound was effected with stannous chloride and hydrogen chloride in acetic acid solution.⁴

Experimental Part

1-Ethyl 2-(β -Diethylaminoethyl) 3-Nitrophthalate Hydrochloride

Method A.—3-Nitrophthalic acid⁵ (IV) was converted into 1-ethyl 3-nitroacidphthalate⁶ (V). A solution of 11.9 g. (0.050 mole) of the highly purified monoester and 6.5 g. (0.048 mole) of β -diethylaminoethyl chloride⁷ in 30 cc. of isopropyl alcohol, which had been treated with sodium and distilled, was refluxed for twelve hours. The solvent was removed by distillation under reduced pressure and the

(3) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

(4) Blicke and Parke, *This Journal*, **61**, 1201 (1939).

(5) "Organic Syntheses," Coll. Vol. I, p. 399.

(6) Cohen, Woodroffe and Anderson, *J. Chem. Soc.*, **109**, 232 (1916). These investigators also described the 1-methyl and the 1-propyl ester.

(7) The chloroethyl hydrochloride has been described by Slotta and Belmisch, *Ber.*, **68**, 758 (1935). The base was liberated from an aqueous solution of the hydrochloride and used immediately.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by Chieko Otsuki in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) (a) Pyman, *J. Chem. Soc.*, **93**, 1796 (1908); (b) see also German Patent 371,046 (*Frdl.*, **14**, 1244).