the second experiment, and $[Br_3^-]$ would be 0.0494. The constant K, therefore, lies between $(0.00206 \times 0.0506)/0.0494 = 0.00211$ and the value 0.00429, obtained by a similar calculation on the first run. With equilibration so slow, it would be difficult to obtain great accuracy in these measurements. Our working value of 0.0024 was obtained by interpolation on the basis of the apparent extent of bromine migration in the two experiments.

Acknowledgment.—We thank Mr. T. P. Palmer for valuable aid in the integration of Eq. (2) and its application to the experimental data.

Summary

1. The rate of bromination of stilbene in methyl alcohol solution is sharply diminished by bromide ions, but not by hydrogen ions.

2. Therefore, although stilbene methoxy bromide is the principal product of the reaction, methyl hypobromite is not responsible for its formation.

3. The kinetics of the reaction is consistent with a mechanism of reaction in two steps, in which molecular bromine is the active agent.

4. The kinetics of the reaction is inconsistent with any mechanism attributing the principal activity to methyl hypobromite catalyzed by acids, or to a positive bromine ion.

5. A general theory of halogenation in polar solvents is briefly discussed.

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

Synthesis of Compounds with Hypnotic Properties. I. Alkoxymethylhydantoins[1]

BY NEIL E. RIGLER WITH HENRY R. HENZE

Rather striking evidences of the relationship of physiological action to chemical constitution have been demonstrated in the relation of isomerism and molecular weight of the simple alkyls to soporific power.[2] In this respect the series of alkyl disubstituted barbituric acids has been most thoroughly investigated and studies of a large number of these compounds have resulted in the synthesis of several soporifics of definite potency and usefulness. The heterocyclic compound hydantoin, which is structurally related to barbituric acid, has been chosen as an innocuous substance which might be converted into soporific derivatives by the attachment to the nucleus of suitable alkyl, alkyloxy, aryl, or aryloxyalkyl groups. The derivatives of hydantoin have been but briefly investigated and one of them, phenylethylhydantoin, Nirvanol, has been demonstrated to be of considerable value in the treatment of chorea and other nervous disorders.[3] In our research the groups attached to the hydantoin nucleus, either directly or through the methoxy grouping, were those which have been demonstrated to possess a definite narcotic effect. The combinations of alkyls chosen were such that the total number of carbon atoms (10 or 11) was that known to be most effective among the barbiturates.[4] However, an additional variation was obtained by having one of the alkyls attached, not directly to the nuclear carbon, but indirectly through the methoxyl group, so that the compounds prepared are 5,5′-alkoxymethyl alkyl (or aryl) hydantoins. It was hoped that in some one compound of this type the soporific properties might be of the same order as those of the newer barbiturates while at the same time any appreciable deleterious effects upon the system would be absent.

For obtaining the hydantoins desired, a method of preparation from ketones developed by Read,[5] and recently used by Herbst and Johnson,[6] was chosen. The alkoxy ketones required were synthesized from chloro ethers according to the method previously described.[7] The entire process may be represented as follows

(1) From a dissertation presented by Neil E. Rigler 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, 1935.

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

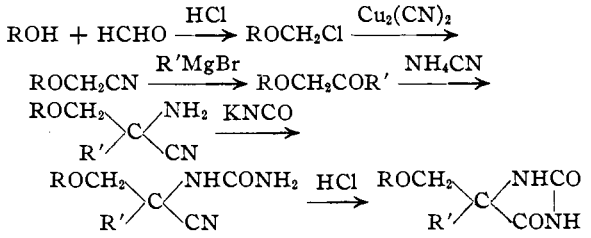
(3) De Rudder, *Chem. Zentr.*, **99**, I, 2628 (1926); Poynton and Schlesinger, *Lancet*, II, 267 (1929); Pilcher and Gerstenberger, *Am. J. Diseases Children*, **40**, 1239 (1930); Jones and Jacobs, *J. Am. Med. Assoc.*, **99**, 18 (1932).

(4) Carnot and Tiffeneau, *Compt. rend.*, **175**, 241 (1922); Dox, *J. Am. Pharm. Assoc.*, **12**, 602 (1923); ref. 2.

(5) Read, THIS JOURNAL, **44**, 1746 (1922).

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

(7) Henze and Rigler, *ibid.*, **56**, 1350 (1934).



When the investigation was practically complete, there became available the work of Bergs[8] and of Bucherer and co-workers[9] in which a method was described whereby hydantoins were prepared directly from ketones by the action of ammonium carbonate and potassium cyanide in alcoholic solution. Hence, four of the six alkoxymethyl hydantoins were resynthesized to compare the newer with the older method.

Experimental

Alkoxyacetonitriles from Chloro Ethers.—The alkoxyacetonitriles necessary were prepared from the corresponding chloro ethers by a modification of the method of Gauthier.[10] One-third its volume of anhydrous benzene was added to the chloro ether; the cuprous chloride formed in the course of the reaction was largely insoluble in the resulting solution and was readily removed by filtration. The physical data for the ethoxyacetonitrile and isoamyloxyacetonitrile are listed in Table I.

TABLE I

ALKOXYACETONITRILES, R—O—CH_2CN

R	B. p., (corr.) °C.	Mm.	d^{20}_4	$n^{20}D$	MR Calcd.	MR Obsd.	Yield, %
Ethyl[a]	134–135	755	0.9168	1.3898	22.06	21.98	83
i-Amyl[a]	186–187	753	.8796	1.4130	35.91	36.03	81

[a] Gauthier, *Ann. chim. phys.*, [8] **16**, 289 (1909).

Preparation of Alkoxymethyl Alkyl Ketones.—The desired ketones were obtained by the Grignard reaction from alkoxyacetonitriles as described by us elsewhere.[7] The physical data and the analyses of the six ketones prepared during this investigation are presented in Table II.

Preparation of Alkoxymethyl Amino-acetonitriles.—The alkoxy ketones were converted into the corresponding amino-nitriles by the action of anhydrous hydrogen cyanide and gaseous ammonia according to the procedure described by Herbst and Johnson.[6] However, anhydrous methyl alcohol was found to be equally as suitable as anhydrous ethyl alcohol and was used on account of its greater availability. The hydrogen cyanide was prepared and stored according to the technique of Ziegler.[11] An excess of hydrogen cyanide seemingly did not shift the equilibrium in the direction of nitrile formation but merely caused the production of resinous material since, even on long standing, all of the ketone was not converted into the amino-nitrile.

Although Read's method, as modified by Herbst and Johnson, gave satisfactory results, the stability of the amino-nitriles suggested the possibility of their formation from the ketones by the action of ammonium chloride and potassium cyanide as used by Zelinsky and Stadnikoff[12] in the production of aliphatic nitriles. While the yields were slightly less than those obtained by the use of Read's method, the handling of toxic prussic acid and of gaseous ammonia was avoided. However, the substitution of ammonium sulfate for ammonium chloride increased the yield. Since here, too, the production of the amino-nitrile was not complete, a slight excess of ammonia, supplied in the form of concentrated ammonia water, also exerted a favorable influence upon the yield. For example, isoamyloxymethyl ethyl aminoacetonitrile was prepared in 89% yield by adding to a methanol solution of the ketone a saturated solution containing equivalent quantities of potassium cyanide, ammonium sulfate and ammonium hydroxide. After two days had elapsed the precipitate was removed by filtration and the amino-nitrile and unreacted material separated by the customary acid treatment. An additional quantity of amino-nitrile was obtained by allowing the acid insoluble material to stand for several hours in contact with concentrated ammonium hydroxide solution, and was added to that first obtained. Ethoxymethyl phenyl ketone was also converted to the corresponding amino-nitrile by this procedure, but in only 45% yield. This behavior confirms the experience of Read, who found that the presence of water in the solvent decreases the yield when an aryl ketone is used. It was also possible to prepare the amino-nitriles without the presence of water by refluxing a mixture of ammonium chloride, potassium cyanide and a methanol

TABLE II

ALKOXY KETONES, R—O—CH_2CO—R′

R	R′	B. p., (corr.) °C.	Mm.	d^{20}_4	$n^{20}D$	Yield, %	MR Calcd.	MR Obsd.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl	*i*-Amyl[a]	185–186	752	0.8042	1.4210	71	40.79	40.71	...	...	...	...
Ethyl	*i*-Amyl[b]	105–106	35	.8797	1.4212	47	45.42	45.30	...	...	...	...
Ethyl	*s*-Butyl	172–173	743	.8882	1.4158	28.5	40.79	40.71	66.62	66.10	11.19	11.04
Ethyl	Phenyl[b]	120–122	15	1.0552	1.5250	68	47.98	47.63	...	...	...	...
Ethyl	Ethyl[b]	146–147	752	0.9139	1.4068	84	31.56	31.30	...	...	...	...
i-Amyl	Ethyl	196–197	752	.8822	1.4192	82	45.42	45.28	68.29	67.98	11.47	11.60

[a] Henze and Rigler, THIS JOURNAL, **56**, 1350 (1934). [b] Sommelet, *Ann. chim. phys.*, [8] **9**, 484 (1906).

(8) German Patent 566,094.

(9) 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).

(10) Gauthier, *Ann. chim. phys.*, [8] **16**, 289 (1909).

(11) Ziegler, "Organic Syntheses," Collective Volume I, 1932, p. 307.

(12) Zelinsky and Stadnikoff, *Ber.*, **39**, 1722 (1906).

TABLE III

ALKOXYMETHYL ALKYL AMINO-ACETONITRILES, $R—O—CH_2—\underset{R'}{\overset{CN}{C}}—NH_2$

R	R'	d^{20}_4	$n^{20}D$	MR Calcd.	MR Obsd.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	*i*-Amyl	0.9265	1.4445	48.58	48.53	89	63.48	63.32	10.66	10.81	16.46	16.21
Ethyl	*i*-Amyl	.9126	1.4403	53.20	53.23	97	65.21	65.27	10.91	10.84	...	...
Ethyl	*s*-Butyl	.9358	1.4461	48.58	48.49	81	63.48	63.20	10.66	10.66	16.46	16.52
Ethyl	Ethyl	.9500	1.4376	39.34	39.24	69	59.11	58.95	9.93	10.02	19.69	19.68
i-Amyl	Ethyl	.9116	1.4403	53.20	53.29	89	...	...	...	...	...	...
Ethyl	Phenyl	....	....	...	...	67	...	...	...	...	...	...

solution of the ketone. Decomposition of the amine is inappreciable at this temperature (65–70°) but on prolonged heating in a sealed tube at 95–110° there results only dark brown tarry matter. While the aryl amino-nitrile was a dark brown, somewhat unstable oil, no attempt being made at an analysis or determination of physical properties, all of the alkyl amino-nitriles were isolated in a form sufficiently pure for analytical purposes, determination of physical properties and for use in further syntheses.

Although the acetylamino and benzoylamino derivatives are satisfactory for characterization of certain of the amines, the products of the reaction with phenyl isocyanate in general are more satisfactory since their melting points are higher than those of the corresponding acyl compounds. Such derivatives of the amino-nitriles are listed in Tables IV and V, while the pertinent data for the alkoxy amino-nitriles may be found in Table III. The hydrochlorides of the aminoacetonitriles were found to be unsatisfactory for purposes of characterization.

TABLE IV

ALKOXYMETHYL ACYLAMINO-ACETONITRILES,

$$R—O—CH_2—\underset{R'}{\overset{CN}{C}}—NHCOR''$$

R	R'	R''	M. p., °C. (corr.)	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	*i*-Amyl	Phenyl	103	10.20	10.18
Ethyl	*i*-Amyl	Phenyl	66	9.72	9.37
Ethyl	Phenyl	Phenyl	164	9.52	9.57
Ethyl	Phenyl	Methyl[a]	164–165	12.07	12.22

[a] Calcd.: C, 67.24; H, 6.90. Found: C, 67.15; H, 7.17.

TABLE V

ALKOXYMETHYL PHENYLUREIDO-NITRILES

$$R—O—CH_2—\underset{R'}{\overset{CN}{C}}—NHCONHC_6H_5$$

R	R'	M. p., °C. (corr.)	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	*i*-Amyl	151–151.6	14.52	14.28
Ethyl	*i*-Amyl	138	13.85	13.62
Ethyl	*s*-Butyl	119–119.5	14.52	14.49
Ethyl	Phenyl[a]	167	...	...

[a] Calcd.: C, 69.90; H, 6.20. Found: C, 69.94; H, 6.29.

Formation of Ureido-nitriles.—In obtaining the ureido-nitriles the preliminary conversion of the amino-nitrile into the hydrochloride, as practised both by Biltz and Slotta[13] and by Herbst and Johnson,[6] is apparently unnecessary. To the amino-nitrile dissolved in 3 to 4 times its volume of 70% acetic acid in a flask was added slowly and with shaking twice the equivalent quantity of powdered potassium cyanate. The mixture was then warmed at 65–70° for one hour and the solution poured into three volumes of water. After several hours the supernatant liquid solidified and was recrystallized to form, with two exceptions, colorless needles. An additional quantity of solid was obtained after making the solution alkaline with ammonium hydroxide. Water was found to be the best medium for recrystallization, although not entirely satisfactory on account of the great solubility of the ureido-nitriles in it. The ureides were very soluble in all common organic solvents except petroleum ether. Appropriate physical data for the compounds of this type are listed in Table VI.

Formation of Hydantoins.—The ureido-nitriles were readily soluble in an excess of 20% hydrochloric acid and upon heating the solution on the steam-bath the corresponding hydantoins settled out almost immediately. After reaction was complete the hydantoin was filtered off, washed with cold water and recrystallized from hot alcohol of the necessary strength.

When the ureido-nitrile, of the corresponding hydantoic acid, was formed in poor yield or isolated with difficulty, it was found advantageous to omit the separation of this intermediate compound. A smaller proportion of acetic acid was used as a solvent for the amino-nitrile and after addition of cyanate and warming for the customary length of time, a sufficient quantity of hydrochloric acid was added to make the resulting solution 20% in hydrogen chloride. Upon heating on the steam-bath, crystals of hydantoin separated and, after dilution, were filtered as usual.

Synthesis of hydantoins directly from alkoxy ketones was accomplished by treatment with ammonium carbonate and potassium cyanide according to the directions of Bucherer.[9] To an Erlenmeyer flask equipped with an air condenser were added 0.13 mole of potassium cyanide, 0.3 mole of freshly powdered ammonium carbonate, and a solution of 0.1 mole of the ketone in 7–8 times its volume of 50% alcohol. The mixture was shaken well and then warmed on a water-bath at 55–60° for about seven hours. The cyanide and carbonate gradually dissolved with evolution of gas and deposition of ammonium carbonate crystals in the condenser. In order to precipitate the hydantoin most of the alcohol was removed by evaporation and the solution allowed to cool. An additional crop of very small crystals was obtained by acidifying the solution with hydrochloric acid.

The hydantoins are easily recrystallized as finely granular, colorless particles. They are soluble in the common

(13) Biltz and Slotta, *J. prakt. Chem.*, [2] **118**, 233 (1926).

TABLE VI

ALKOXYMETHYL UREIDO-NITRILES, $R—O—CH_2—\underset{R'}{\overset{CN}{C}}—NHCONH_2$

R	R′	M. p., °C. (corr.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	*i*-Amyl	127–128	69	56.30	56.10	8.98	9.06	19.70	19.61
Ethyl	*i*-Amyl	126.5	66	58.15	58.28	9.32	9.42	18.50	18.71
Ethyl	*s*-Butyl	113.5–114.5	53	56.30	56.21	8.98	8.98	19.70	19.54
Ethyl	Phenyl	167	71	61.91	61.77	6.49	6.63	18.01	18.29
Ethyl	Ethyl	liquid	58	...	...	..	..	...	...
i-Amyl	Ethyl	liquid	82	...	...	..	..	...	...

TABLE VII

ALKOXYMETHYL HYDANTOINS, $CO—NH$ / $CH_2—O—R$ / C / R' / $NH—CO$

R	R′	M. p., °C. (corr.)	Yield, %[a] A	B	C	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	*i*-Amyl	195–196	85	86	..	56.04	56.02	8.47	8.49	13.07	12.95
Ethyl	*i*-Amyl	179–180	86	..	..	57.84	58.02	8.85	8.99	12.28	12.42
Ethyl	*s*-Butyl	164.5–165	77	55	87	56.04	55.84	8.47	8.36	13.07	13.01
Ethyl	Ethyl	147–148	43	57	66	51.58	51.85	7.58	7.76	15.04	15.20
i-Amyl	Ethyl	107–108	85	68	81	57.84	58.07	8.85	9.00	12.28	12.58
Ethyl	Phenyl	191.5	90	..	79	61.51	61.34	6.03	5.87	11.96	12.36

[a] Methods of preparation: (A) From the ureido-nitrile. (B) From the amino-nitrile, without isolation of the ureide. (C) From the ketone by Bucherer's method.

organic solvents but, with one exception, only very slightly soluble in water. However, they dissolve in aqueous solutions of alkalies and are reprecipitated unchanged upon addition of an excess of acid. The alkoxymethylhydantoins are stable compounds, melting without decomposition to straw colored liquids. The data for the characteristic physical properties of the six new hydantoins are collected in Table VII.

Sodium Salts of the Hydantoins.—The sodium salts were prepared by dissolving an hydantoin in an equivalent quantity of 1 *N* alcoholic sodium hydroxide and pouring the solution into an excess of ether, the salt precipitating as a colorless, crystalline solid. The sodium salts, although readily soluble in water, are but slightly hygroscopic.

Pharmacological Report

The ethoxymethylphenylhydantoin and isoamyloxymethylethylhydantoin, in the form of their sodium salts, have been subjected to a preliminary pharmacological testing by Dawson and Taft.[14] Of these two compounds, the former in moderate doses causes convulsions and for it the range between the effective and lethal doses is too narrow; the latter is less toxic, producing no convulsions, but requires too large a dose to be recommended for use as a satisfactory soporific.

Summary

The preparation of 5,5′-hydantoin derivatives has been extended to include those containing alkoxyl groups. These hydantoins have been prepared in three different ways, the action of ammonium carbonate and potassium cyanide on the corresponding ketone being shown to be simplest, most direct and productive of the highest yields.

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(14) The authors desire to express their appreciation to Professor W. T. Dawson and Associate Professor C. H. Taft, of the Department of Pharmacology, Medical School, University of Texas, for making these tests.