The present study provides a more scientific basis for these ratios and correlates them with sugar structure.

Summary

1. Quantitative studies have been made of the oxidation of twenty-five sugars by *d*-, *l*- and *meso*-tartrate modifications of the Folin–Wu alkaline copper reagent and by Sumner's dinitrosalicylate reagent.

2. The behavior of reducing sugars is determined by the entire sugar molecule, but intramolecular influences can be conveniently classified as planar and extraplanar, *cis–trans* relations being important extraplanar influences.

3. Epimeric sugars have related behaviors, the glucose epimeric system being most symmetrical in all dimensions. *cis*-Sugars are most unsymmetrical in a planar sense and methylpentoses in an extraplanar sense.

4. *meso*-Tartrate reagent is susceptible to both planar and extraplanar influences.

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Hydantoins Derived from the Analogs of 1,3-Dichloroisopropoxyethyl Methyl Ketone[1]

BY BRUCE B. ALLEN WITH HENRY R. HENZE

As a continuation of attempts to prepare substances possessing soporific properties, attention has now been directed to the synthesis of 5,5-disubstituted hydantoins in which one of the substituents is of the halogenoalkoxyalkyl type. In this Laboratory, the application of Bucherer's[2] hydantoin synthesis has been extended to the preparation of disubstituted heterocyclic compounds from such bifunctional carbonyl substances as alkoxymethyl alkyl (or aryl) ketones[3] and phenoxymethyl alkyl (or aryl) ketones,[4] and has been shown to be advantageous over other accepted methods as regards yield, ease of execution, and degree of purity of product. In the present investigation, then, successful use of the Bucherer method in hydantoin formation from dichloroisopropoxyethyl alkyl or aryl ketones resulted in further extension of the application of the method. The ketones used were, with one exception, of the type $(CH_2Cl)_2CH\text{-}O\text{-}CH(CH_3)\text{-}COR$ where R represents alkyl and includes those groups which have been shown most active physiologically; the preparation and characterization of these ketones have been described by us previously.[5] Since the hydantoin derived from the phenyl analog of this series of ketones represents a halogenoalkoxyl derivative of Nirvanol (5-ethyl-5-phenylhydantoin), a substance shown to possess useful medicinal value,[6] it was deemed pertinent to effect its preparation and subsequent conversion into the corresponding hydantoin.

Experimental

Preparation of α-1,3-Dichloroisopropoxyethyl Alkyl Ketones.—The eight ketones of this series which were employed were prepared from α-1,3-dichloroisopropoxypropionitrile by means of the Grignard reaction, these preparations having been described previously.[5]

Preparation of α-1,3-Dichloroisopropoxyethyl Phenyl Ketone.—The general method as described for the preparation of the alkyl analogs was employed in the synthesis of this ketone. The Grignard reagent from 48.1 g. (0.31 mole) of phenyl bromide, 7.3 g. (0.3 atom) of magnesium in the form of turnings, and 250 cc. of anhydrous ether was treated with the solution of 45.5 g. (0.25 mole) of α-1,3-dichloroisopropoxypropionitrile in an equal volume of ether. Although vigorous reaction occurred throughout the nitrile addition, completion was ensured by refluxing for two hours over a steam-cone. The addition product, which separated as a gray-colored solid, was decomposed in the usual manner with chilled, dilute hydrochloric acid and crushed ice; the resulting ether layer was separated, washed with dilute sodium carbonate solution and then water, and finally dried over anhydrous calcium chloride. The crude material was freed of ether by evaporation and then purified by two fractionations under 4 mm. pressure; the pure ketone is a colorless, almost odorless, quite viscous liquid which develops a deep red coloration upon standing; yield, 45.4 g. (69.6%); b. p. 169° (4 mm.); d^{20}_4 1.2356; $n^{20}D$ 1.5398; *MR* calcd., 66.18;[7] *MR* found, 65.31; γ^{20} 35.53 dynes/cm.; *P* calcd. (Sugden's atomic constants), 538.4; *P* found, 516.0.

(1) From a portion of a dissertation presented by Bruce B. Allen 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) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

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

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

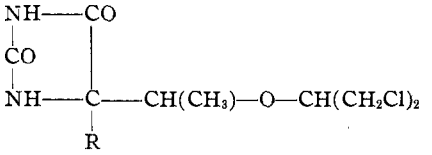
(5) Allen with Henze, *ibid.*, **59**, 540 (1937).

(6) 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).

(7) This summation includes the exaltation value due to the C_6H_5-CO- grouping which has been determined for acetophenone by Auwers and Eisenlohr, *J. prakt. Chem.*, [2] **84**, 20 (1911).

TABLE I

5-[1-(2-CHLORO-1-CHLOROMETHYLETHYL)-OXY]-ETHYL-5-ALKYL OR PHENYLHYDANTOINS



-R	M. p., °C. (corr.)	Yield, %	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-CH_3$	229.0–230.0	85.6	26.35	26.38	10.41	10.66
$-CH_2CH_3$	198.5–199.5	84.2	25.05	25.22	9.89	9.92
$-CH_2CH_2CH_3$	211.5–212.5	69.5	23.86	23.97	9.43	9.56
$-CH(CH_3)_2$	146.5–147.5	66.2	23.86	24.09	9.43	9.43
$-CH_2CH_2CH_2CH_3$	206.5–207.5	75.4	22.79	22.70	9.00	9.11
$-CH(CH_3)CH_2CH_3$	149.5–151.0	43.2	22.79	22.79	9.00	8.81
$-CH_2CH_2CH_2CH_2CH_3$	181.0–182.0	87.7	21.80	21.56	8.61	8.77
$-CH_2CH_2CH(CH_3)_2$	187.0–187.5	60.0	21.80	21.64	8.61	8.74
$-C_6H_5$	187.0–188.0	79.7	21.41	21.53	8.46	8.47

Anal. Calcd. for $C_{12}H_{14}Cl_2O_2$: Cl, 27.16. Found: Cl, 26.91.

Synthesis of 5-[1-(2-Chloro-1-chloromethylethyl)-oxy]-ethyl-5-alkyl or -5-phenylhydantoins.—Bucherer's method[2] was applied to the formation of this series of compounds: one mole of the appropriate dichloroisopropoxyethyl alkyl or aryl ketone was added to the suspension of 1.25 moles of potassium cyanide and 3 moles of freshly powdered ammonium carbonate in as much 50% alcohol as would approximate seven times the volume of the ketone, and then the resulting mixture heated from six to eight hours in a flask equipped with an air-condenser and maintained at 55–62°. In most cases, the solid hydantoin began to separate from the warm reaction mixture after heating had continued for three to five hours. After completion of reaction, the mixture was allowed to cool and the solid which had formed was removed by filtration; when the solution was concentrated and again cooled, a second portion of more finely crystalline solid material was obtained. Occasionally, however, the material separating after concentration was in the form of an oil but generally solidified and could then be recrystallized. Finally, acidification of the mother liquor caused separation of still another small amount of solid or oil. Two of the hydantoins, namely, the isopropyl and secondary butyl, failed to conform with this behavior in that there was no separation of material during the reaction period; after concentration of the reaction mixtures to relatively small volumes and acidification, the crude hydantoins separated as dark-colored oils. It was only after prolonged boiling with 20% hydrochloric acid, treatment with Norit, and dissolving in warm alcohol followed by pouring the resulting solutions on crushed ice that the substances were obtained in solid form. The hydantoins could then be recrystallized readily from the usual solvents.

The hydantoins, all white solids, were recrystallized easily from 50–60% alcohol; the butyl and amyl analogs lacked the definite crystalline structure of the lower alkyl and phenyl analogs, separating from the solvent as amorphous solids which were powders when dried, but which possessed sharp melting points. The hydantoins were readily soluble in the organic solvents such as acetone and 95% alcohol and in aqueous alkali, but were quite insoluble in water. The data for melting points, percentage yields, and the analytical results for the nine hydantoins prepared have been summarized in Table I.

It is of interest to note that although the conditions favoring nitrile formation were present during these hydantoin preparations, namely, an alkyl halide in the presence of aqueous-alcoholic potassium cyanide, no replacement of chlorine by cyanide was observed.

Summary

1. The preparation of eight new hydantoins from a series of dichloroisopropoxyethyl alkyl ketones extended the application of Bucherer's method for preparing 5,5-disubstituted hydantoins to include the alkyl halogenoalkoxyalkyl type.

2. From the Grignard reaction, involving interaction of phenylmagnesium bromide and α-1,3-dichloroisopropoxypropionitrile, was obtained the phenyl analog to the dichloroisopropoxyethyl alkyl series of ketones, this synthesis representing the initial preparation of an aryl chloroalkoxyalkyl ketone.

3. The successful conversion of the latter into the corresponding hydantoin further extended the use of Bucherer's method to preparation of a hydantoin of the 5-aryl-5-chloroalkoxyalkyl type and resulted in the formation of a new derivative of the medicinal Nirvanol.

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