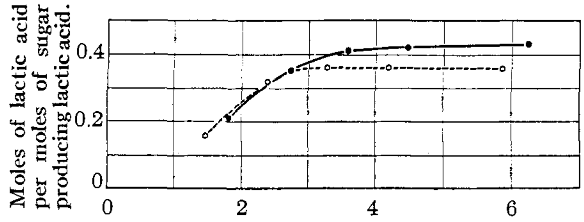
to the effect that only the first and third hexose sections of these trisaccharides will be degraded by the alkali so that lactic acid is a product. The yields of lactic acid are indicative of the general course of these alkaline degradation reactions. As an example, 6-cellobiosidoglucose hendecaacetate is shown in the formula. Sections indicated as (A) and (C) should be sources of lactic acid, while section (B) would be degraded to products other than lactic acid. A similar parallel exists in the case of the other three trisaccharides, all of which produce nearly equal amounts of lactic acid.



Normality of potassium hydroxide.

Fig. 4.—Lactic acid from 0.125 *M* glucose + 0.125 *M* mannose + (11 × 0.125) mole equivalents of $KC_2H_3O_2$ ●——● and from 0.125 *M* 6-maltosido-mannose hendecaacetate ○- - - -○, at 50° for forty-eight hours.

COLUMBUS, OHIO

RECEIVED APRIL 20, 1940

[CONTRIBUTION NO. 188 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

Synthesis of 5,5-Disubstituted Hydantoins from *sym*-Dialkoxypropanones and Related Compounds

BY BURL G. ROGERS AND HENRY R. HENZE

Certain hydantoins of the monoalkoxymethyl type[1] prepared in this Laboratory have been demonstrated to possess definite hypnotic activity; however, of the derivatives tested thus far few are likely to find clinical use. In an effort to obtain a satisfactory soporific of this type, a study has now been made of the synthesis of 5,5-dialkoxymethylhydantoins and related types. The ketones used for conversion into hydantoins are of the symmetrical type, $ROCH_2COCH_2OR'$, where R and R′ represent the same alkyl grouping, or allyl, and include four compounds which have not been described previously.

Since unsymmetrical dialkoxyacetones, in which the two alkyls are not the same, might be expected to yield hydantoins having greater potentiality of soporific value, attention also has been directed to the preparation of these ketones. The method employed for the attempted syntheses was essentially that previously described by us[2]; however, the products obtained were mixtures of ketones that could not be separated by fractional distillation.

Experimental

Preparation of *sym*-Dialkoxypropanols.—These compounds, of type $ROCH_2CHOHCH_2OR$, were prepared by modification of a method described by Fairbourne and collaborators.[3] Data concerning selected physical properties and analytical results are listed in Table I.

Preparation of *sym*-Dialkoxypropanones.—These ketones, of type $ROCH_2COCH_2OR$, were prepared by the oxidation of the corresponding *sym*-dialkoxypropanols; those not reported previously are listed, together with certain data for characteristic physical properties and analyses, in Table II.

Oxidation of the *sym*-diallyloxypropanol, however, gave a mixture of compounds from which the pure *sym*-diallyloxypropanone could not be separated by repeated distillation. Treatment of a fraction, which on the basis of its molecular refraction appeared to be pure, with 2,4-dinitrophenylhydrazine gave a very impure derivative, which after repeated recrystallizations gave a product that analyzed correctly for the 2,4-dinitrophenylhydrazone of *sym*-diallyloxyacetone and melted at 45–46° (cor.).

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: N, 15.99. Found: N, 15.77.

Although some ketone was obtained, as evidenced by the formation of this derivative, it could not be purified by fractional distillation.

Preparation of *unsym*-Dialkoxypropanols.—These compounds of type $ROCH_2CHOHCH_2OR'$, were synthesized from α-chloro-γ-alkoxypropanols according to a procedure described by Fairbourne, *et al.*[4] Two new examples of this type, namely, the methyl ethyl and the methyl *n*-propyl members, were synthesized and their physical and analytical data are included in Table I.

Attempted Preparation of *unsym*-Dialkoxypropanones.—The procedure employed for the synthesis of these ketones, having the formula $ROCH_2COCH_2OR'$, already has been described for the preparation of the *sym*-dialkoxypropanones. In every case the oxidation of the *unsym*-propanols produced mixtures of ketones from which were obtained mixtures of 2,4-dinitrophenylhydrazones that could not be separated by repeated recrystallizations. Analyses of

---

[1] Rigler with Henze, THIS JOURNAL, **58**, 474 (1936).

[2] Henze and Rogers, *ibid.*, **61**, 433 (1939).

[3] Fairbourne, Gibson and Stephens, *J. Chem. Soc.*, 445 (1931).

[4] *Ibid.*, 1865 (1932).

TABLE I

DIALKOXYPROPANOLS

Compounds	B. p. °C. (cor.)	B. p. Mm.	Yield, %	d^{20}_4	n^{20}_D	Mol. refraction Calcd.	Mol. refraction Found	ΔMR	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$(n\text{-}C_6H_{13}OCH_2)_2CHOH$[a]	141–142	3	52	0.8978	1.4401	76.28	76.46	+0.18	69.18	69.21	12.39	12.55
$(n\text{-}C_7H_{15}OCH_2)_2CHOH$	160–161	5	42	.8911	1.4430	85.52	85.82	+ .30	70.78	70.81	12.58	12.56
$(n\text{-}C_4H_9\text{-}CH(C_2H_5)CH_2OCH_2)_2CHOH$[b]	162–163	5	14	.8957	1.4471	94.75	94.43	− .32	72.10	71.84	12.74	12.46
$(C_3H_5OCH_2)_2CHOH$[c,d]	124–125	24	80	.9832	1.4539	47.64	47.43	− .21	62.76	62.48	9.37	9.41
$C_2H_5OCH_2CHOHCH_2OCH_3$	56–57	8	50	.9817	1.4212	34.72	34.67	− .05	53.71	53.40	10.52	10.30
$n\text{-}C_3H_7OCH_2CHOHCH_2OCH_3$	59–60	5	70	.9596	1.4240	39.34	39.41	+ .07	56.73	56.81	10.88	10.79

[a] Zunino, *Atti. accad. Lincei,* [5] **9**, I, 310 (1900), reported b. p. 180°; d^{15} 0.987 for a compound prepared from epichlorohydrin, potassium hydroxide and an alcohol which he stated to be "l' alcool caprilico di fermentazione od essilico che bolle a 150°. La sua costituzione non è ben conosciuta, ma si ammette che sia primario poichè per ocsidazione dá l'acido caproico." [b] *Ibid.*, [5] **9**, I, 311 (1900), reported the synthesis of the dioctyloxypropanol by the same method and listed b. p. 224°, d^{15} 0.990. [c] Kishner, *J. Russ. Phys.-Chem. Soc.*, [1] 31 (1892); through *Ber.*, **25**, Referate 506 (1892), reported this preparation from sodium allylate and epichlorohydrin and listed b. p. 225–227°, d^0 0.9972. [d] Zunino, *Atti. accad. Lincei.*, [5] **6**, II, 348 (1897), reported this preparation by the action of potassium hydroxide on epichlorohydrin in an allyl alcohol solution and listed b. p. 225–227°, d^{21} 0.991.

TABLE II

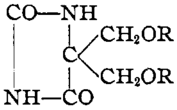
sym-DIALKOXYPROPANONES

Compounds	B. p. °C. (cor.)	B. p. Mm.	Yield, %	d^{20}_4	n^{20}_D	Mol. refraction Calcd.	Mol. refraction Found	ΔMR	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$(n\text{-}C_6H_{13}OCH_2)_2CO$	135–136	5	46	0.9072	1.4388	74.77	74.88	+0.11	69.72	69.43	11.70	11.68
$(n\text{-}C_7H_{15}OCH_2)_2CO$	187–188	10	55	.9000	1.4421	84.00	84.23	+ .23	71.28	71.02	11.96	12.21
$(n\text{-}C_4H_9\text{-}CH(C_2H_5)CH_2OCH_2)_2CO$	162–164	5	50	.9009	1.4454	93.24	92.98	− .26	72.56	72.18	12.18	12.07
$(C_3H_5OCH_2)_2CO$[a]	118–120	24	52	.9997	1.4538	46.13	46.09	− .04	63.51	61.85	8.29	8.72

[a] The yield of this compound is based upon the quantity of material obtained from the reaction mixture and is not intended to represent the yield of the pure ketone. All other physical and analytical data listed here represent those of a fraction which appeared to be relatively pure.

TABLE III

DIALKOXYMETHYLHYDANTOINS



—R	M. p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$—CH_3$	214.0–215.0	11.0	44.68	44.85	6.43	6.39	14.89	14.83
$—CH_2CH_3$	180.5–181.5	24.0	49.99	49.70	7.46	7.53	12.96	12.86
$—CH_2CH_2CH_3$	104.5–105.5	17.0	54.08	54.40	8.25	8.11	11.47	11.68
$—CH_2CH_2CH_2CH_3$	98.5– 99.5	24.0	57.33	57.34	8.88	9.02	10.29	10.51
$—CH_2CH(CH_3)_2$	173.0–174.0	11.0	57.33	57.45	8.88	9.06	10.29	10.17
$—CH(CH_3)CH_2CH_3$	222.0–223.0	2.0	57.33	57.09	8.88	9.02	10.29	10.43
$—CH_2CH_2CH_2CH_2CH_3$	103.5–104.5	15.0	59.97	59.73	9.40	9.60	9.33	9.31
$—CH_2CH_2CH(CH_3)_2$	146.0–147.0	22.0	59.97	60.11	9.40	9.47	9.33	9.33
$—CH_2CH_2CH_2CH_2CH_2CH_3$	82.5– 84.0	37.0	62.16	62.41	9.82	9.83	8.53	8.74
$—CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	71.0– 73.0	39.0	64.01	64.20	10.18	10.39	7.86	7.66
$—CH_2CH{=}CH_2$	107.5–108.5	0.5[a]	...	...	...	...	11.66	11.62

[a] Yield based on impure ketone.

these derivatives gave values which indicated that they were derived from a mixture of ketones. Since repeated fractionation failed to yield a pure ketone, even through the efficient column of Lesesne and Lochte,[5] the synthesis of these propanones was abandoned.

Synthesis of 5,5-Dialkoxymethylhydantoins.—The formation of the hydantoins of this series was accomplished through use, in general, of 0.10 mole of ketone, 0.13 mole of potassium cyanide, 0.3 mole of ammonium carbonate, and a quantity of 50% alcohol approximately equal to seven times the volume of the dialkoxyacetone.

In the preparation of *n*-butoxy-, *s*-butoxy-, and *n*-amoxy- analogs, the usual procedure was deviated from in that the reaction mixtures were heated in a bomb for six hours at 100°. In the synthesis of *n*-hexyloxy- and *n*-heptyloxyhydantoins the yield appeared to have been improved by using somewhat greater amounts of potassium cyanide and ammonium carbonate, namely, 0.04 mole of potassium cyanide and 0.08 mole of ammonium carbonate per 0.02 mole of ketone.

No hydantoin could be obtained from *sym*-di-*s*-propoxypropanone or *sym*-di-2-ethylhexyloxypropanone even after repeated attempts under varying conditions.

The hydantoins obtained were placed in alcohol and treated with Norit Crystallization was induced by the addition of water and chilling in an ice-bath. They are soluble in common organic solvents, but, with the exception of the two lower homologs, quite insoluble in water.

---

[5] Lesesne and Lochte, *Ind. Eng. Chem., Anal. Ed.*, **10**, 450 (1938).

The melting points, percentage yields, and analytical results for the eleven new hydantoins prepared have been collected in Table III.

Summary

1. *sym*-Di-allyloxypropanol and three representatives of the *sym*-alkoxypropanol series have been prepared, one of which, the *sym*-di-*n*-heptyloxypropanol, has not been previously reported in the literature.
2. Three new members of the *sym*-dialkoxypropanone type of compounds have been prepared, and, in addition, the *sym*-diallyloxypropanone has been synthesized—not, however, in an analytically pure state.
3. Two new members of the *unsym*-dialkoxypropanol series have been synthesized and adequately characterized.
4. Attempts to obtain pure *unsym*-dialkoxypropanones resulted in failure.
5. Utilizing the series of ten *sym*-dialkoxypropanones and *sym*-diallyloxypropanone, Bucherer's method has been extended by the synthesis of eleven hydantoins of a new type.

AUSTIN, TEXAS RECEIVED FEBRUARY 8, 1940

[CONTRIBUTION NO. 171 FROM THE BIOLOGICAL RESEARCH LABORATORIES OF MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Studies in the Activation in Sterols

BY JOHN W. M. BUNKER, ROBERT S. HARRIS AND L. MALCOLM MOSHER

The two important provitamins D in nature are ergosterol and 7-dehydrocholesterol. Is there a difference in their activation by ultraviolet light?

To find an answer to this question we have irradiated ether solutions of crystalline preparations of these provitamins with measured doses of substantially monochromatic ultraviolet through a large quartz monochromator. The activated products have been fed concurrently to large groups of rachitic animals and data sufficient to warrant statistical evaluation have been obtained.

Activation of Ergosterol.—The procedure for the irradiation of ergosterol has been published.[1] Since each irradiation yielded activated sterol sufficient for the feeding of only ten experimental animals, the irradiation procedure was repeated five times for each wave length. The repetitive irradiations were scattered at random through the whole series to distribute any undetected variations in attendant conditions. Each rat was fed an equivalent of 8 mg. of ergosterol that had been exposed to 300×10^{12} quanta, which recent experience showed to be appropriate for the severity of rickets at that time. By the use of a large number of animals in each group in a concurrent test, 48 or 49 observations were obtained for each of the five wave lengths studied.

In an earlier publication[1] we concluded that "the photochemical activation of ergosterol in ether by monochromatic light of 2537, 2652, 2804, 2967 or 3025 Å. is substantially uniform per quantum of energy applied," and in our discussion we confessed to an impression that 2804 Å. appeared to be very slightly more efficient. By statistical analysis this tendency could not be proved to be significant.

In a confirmatory test herein reported, line 2537 Å. was replaced by 2894 Å. because the latter wave length is of much more physiological importance, being at the edge of the solar spectrum while 2537 Å. is in the abiotic region of the ultraviolet, and also because the new line fills in the gap between 2804 and 2967 Å., a region particularly interesting.

A summary of our findings is presented in Table I. The spread in the response of the animals in each group to identical feedings of antirachitic substance is reasonable for the bioassay. However, the concentration of the consistent responses at a mode for each group presents a picture unusually favorable for statistical analysis. The apparent similarity in response which is indicated by the arithmetic means was tested for reality by the "*t*" test[2] which is statistically appropriate for the study of this type and volume of data.

The data essential to the interpretation of the "*t*" test are presented in Table II. A "*t*" value of 2.5 has a probability of 19 out of 20 chances of being a real difference. This analysis indicates that the activation of ergosterol by 3025 Å. is decidedly less efficient than by the other lines tested

---

[1] Harris, Bunker and Mosher, THIS JOURNAL, **60**, 2579 (1938).

[2] Bunker, Harris and Mosher, *ibid.*, **62**, 508 (1940).