groupings appropriate to produce additional derivatives of importance as soporifics or anticonvulsants. Since it is known that the ethyl and *s*-butyl groups are of special physiological potency, it seemed of interest to prepare a series of hydantoins containing these groups connected in an alkoxyalkyl linkage, namely, as the *s*-butoxyethyl grouping. While the preparation of analogous and in a few cases isomeric hydantoins has been accomplished previously, the procedure of Bucherer[1] has not been utilized for the synthesis of 5-(*s*-butoxyethyl)-5-alkyl (or aryl) hydantoins.

Experimental

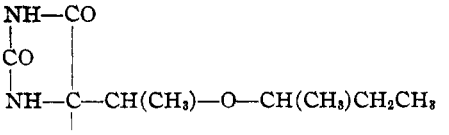
Preparation of α-(*s*-Butoxy)-ethyl Alkyl Ketones.—The nine ketones used as intermediates in the production of the butoxyethyl hydantoins were prepared by the interaction of the appropriate Grignard reagents and *s*-butyl α-cyanoethyl ether as described previously.[5]

Synthesis of 5-[α-(*s*-Butoxy)]-ethyl-5-Alkyl Hydantoins.—The production of nine members of this series of compounds was accomplished by the interaction of an aqueous alcoholic solution of potassium cyanide and ammonium carbonate with the appropriate butoxyethyl alkyl ketones. One part (0.05 mole) of a ketone was mixed with a suspension of 1.25 parts of potassium cyanide and 3.0 parts of ammonium carbonate in 7–8 volumes of 50% alcohol. Upon warming the mixture to 55–60° for five to six hours, the solids gradually dissolved with evolution of gas, followed in most cases with the separation of the solid reaction product from the warm solution. At the termination of this period of warming the mixture was cooled and the product removed by filtration. Concentration of the filtrate with subsequent acidification yielded additional crystalline material, although in the cases of the *s*-propyl and *s*-butyl derivatives there was considerable tendency toward the formation of oily material. However, in these instances, after solidification of the oil no trouble was experienced in purification by further crystallization.

All of the hydantoins of this series are white crystalline solids soluble in alcohol, acetone, benzene, and chloroform but insoluble in water and petroleum ether. Purification was effected by recrystallization from 50–60% ethyl alcohol or from a benzene–petroleum ether mixture. In some instances treatment with Norite was necessary for complete removal of color. These compounds, in general, possess sharp melting points, fusing to form light straw colored liquids without decomposition. Data for melting points, percentage yields, and the analyses for nitrogen content of these hydantoins are presented in Table I.

TABLE I

5-[α-(*s*-BUTOXY)]-ETHYL ALKYL HYDANTOINS



	—R	M. p., °C. (corr.)	Yield, %	Nitrogen, % Calcd.	Found
1	—CH_3[a]	203–204	36	13.08	13.14
2	—CH_2CH_3	190	41	12.27	12.19
3	—$CH_2CH_2CH_3$	205–206	24	11.56	11.70
4	—$CH(CH_3)_2$	196–197	22	11.56	11.70
5	—$CH_2CH_2CH_2CH_3$	204–205	36	10.93	11.01
6	—$CH_2CH(CH_3)_2$	192	44	10.93	11.00
7	—$CH(CH_3)CH_2CH_3$	189–190	30	10.93	10.89
8	—$CH_2CH_2CH_2CH_2CH_3$	178	31	10.36	10.36
9	—$CH_2CH_2CH(CH_3)_2$	177	40	10.36	10.58

[a] Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47. Found: C, 56.13; H, 8.65.

Summary

The series of 5,5-disubstituted hydantoins, potentially important as soporifics or anti-convulsants, has been extended to include nine new *s*-butoxyethyl alkyl hydantoins.

AUSTIN, TEXAS RECEIVED OCTOBER 16, 1939

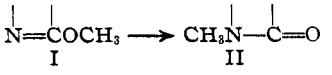
(5) Speer with Henze, THIS JOURNAL, **61**, 1226 (1939).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KWANGSI UNIVERSITY, CHINA]

Researches on Pyrimidines. The Molecular Rearrangement of 4-Methyl-5-*n*-propyl-2,6-dimethoxypyrimidine[1]

BY YUOH-FONG CHI, SHAO-SENG WEI AND MEI-SENG LIANG[2]

Previous publications by Hilbert and Johnson from the Yale laboratories,[3] and later by Chi, Wei and Pan[4] have shown that pyrimidine lactim-ethers of configuration I undergo rearrangement to their isomeric and stable lactam forms II. For example, 2,6-dimethoxypyrimidine and 2-oxy-3-methyl-6-methoxypyrimidine on heating both



I II

underwent rearrangement to 1,3-dimethyluracil. Under similar conditions 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine and 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine are converted to 1,3,4-trimethyl-5-*n*-butyluracil.

(1) This paper is constructed from a dissertation presented by Shao-Seng Wei and Mei-Seng Liang to the Faculty of Kwangsi University as partial fulfilment of the requirements for the degree of Bachelor of Science in June, 1938.

(2) The authors desire to express their appreciation to Professor Treat B. Johnson of Yale University for his assistance in preparing this paper for publication.

(3) Hilbert and Johnson, THIS JOURNAL, **52**, 2001 (1930).

(4) Chi, Wei and Pan, *ibid.*, **60**, 1719 (1938).

In this paper the authors describe the conditions under which 4-methyl-5-*n*-propyl-2,6-dimethoxy-pyrimidine (III) rearranges into (a) 1,3,4-trimethyl-5-*n*-propyluracil (IV) and (b) 2-oxy-3,4-dimethyl-5-*n*-propyl-6-methoxy-pyrimidine (V).

$$\overset{(1)}{N}\text{—}\overset{(2)}{C(OCH_3)}\text{=}N\text{—}\overset{(3)}{C(CH_3)}\text{=}\overset{(4)}{C(C_3H_7)}\text{—}\overset{(5)}{C}\overset{(6)}{(OCH_3)} \quad \text{III}$$

$$CH_3N\text{—}CO\text{—}N(CH_3)\text{—}C(CH_3)\text{=}C(C_3H_7)\text{—}CO \quad \text{IV}$$

$$N\text{—}CO\text{—}N(CH_3)\text{—}C(CH_3)\text{=}C(C_3H_7)\text{—}C(OCH_3) \quad \text{V}$$

The authors have made the observation that the pyrimidine (III) is rearranged smoothly to the lactam modification (IV) by heating at 260–280°. On the other hand, when heated at 50–60° under the catalytic influence of methyl iodide, the partially rearranged pyrimidine (V) is formed. This latter pyrimidine is stable only at low temperatures and undergoes rearrangement at 260–280° to the *lactam* form (IV).

Experimental Part

VI, $NHCONHC(CH_3)\text{=}C(C_3H_7)CO$, 4-Methyl-5-*n*-propyl-uracil.—This pyrimidine was prepared by digesting 4-methyl-5-*n*-propyl-2-thiouracil[5] with chloroacetic acid. Thirty grams of the thiouracil was digested with a solution containing 60 g. of $ClCH_2COOH$ in 150 cc. of water for two hours, whereupon 26 g. of the desulfurized pyrimidine separated as needles, melting at 247–249°. The same pyrimidine also is formed by digesting 2-ethylmercapto-4-methyl-5-*n*-propyl-uracil[5] with strong hydrochloric acid. Twenty-five grams of this mercaptopyrimidine yielded 20 g. of the uracil compound melting at 246–247°.

4-Methyl-5-*n*-propyl-2,6-dichloropyrimidine, VII.—Sixteen and eight-tenths grams of VI was refluxed with 100 cc. of phosphorus oxychloride in an oil-bath at 120–130° until hydrogen chloride gas ceased to be evolved. This took twelve hours. The excess of phosphorus oxychloride was removed by heating the reaction mixture on a water-bath under a vacuum. There was obtained a brown viscous residue which did not solidify. The residue was treated with cracked ice to decompose phosphorus compounds, and then extracted with ether. The ethereal solution was washed with water, dried with calcium chloride and filtered. After distilling the solvent from the ethereal solution, an oil was obtained which was purified by distillation under a vacuum. The pyrimidine VII boils at 163° under 35 mm. pressure, at 149° under 20.8 mm. pressure or at 145–146° under 19.5 mm. pressure, and melts at 31–33°. The yield is 16.4 g. or 80%.

Anal. Calcd. for $C_7H_{10}N_2Cl_2$: N, 13.66. Found: N, 13.9, 13.86.

4-Methyl-5-*n*-propyl-2,6-dimethoxypyrimidine, III.—Four and six-tenths grams of metallic sodium was dissolved in 50 cc. of absolute methyl alcohol. To the cold methyl alcohol solution of sodium methylate, there was slowly added a solution of 20.5 g. of VII in 50 cc. of absolute methyl alcohol. This gave an immediate precipitation of sodium chloride. After the separation of sodium chloride by filtration, the excess of methyl alcohol was distilled off on a water-bath. There remained an oil, which was shaken with 30 cc. of 30% sodium hydroxide solution in which the above pyrimidine was insoluble, and was extracted with ether. The ethereal solution was dried with anhydrous sodium sulfate. The solvent was then distilled off, giving an oil which distilled at 135–140° under 19.5 mm. pressure. The yield was 19.8 g.

Anal. Calcd. for $C_{10}H_{16}O_2N_2$: N, 14.28. Found: N, 14.35, 14.20.

4-Methyl-5-*n*-propyl-2,6-diethoxy-pyrimidine, VIII.—This pyrimidine was prepared by a procedure similar to that used for synthesizing the corresponding dimethoxy-pyrimidine described above. This distilled as a colorless oil, boiling at 145–148° under 18 mm. pressure. The yield was 8.9 g. from 10.2 g. of the corresponding dichloro-pyrimidine.

Anal. Calcd. for $C_{12}H_{20}O_2N_2$: N, 12.49. Found: N, 12.79, 12.88.

Methylation of VI.—(A) Four and two-tenths grams of VI was dissolved in sodium hydroxide solution, containing 2.2 g. of NaOH in 150 cc. of water. To this ice-cooled solution, 5.5 cc. of dimethyl sulfate was added drop by drop while the solution was shaken vigorously. It was then boiled for ten minutes. On cooling, 1,4-dimethyl-5-*n*-propyl-uracil (IX) separated. After recrystallization from benzene and petroleum ether, it melted at 193.5–194°. The yield was 2 g. On mixing with 3,4-dimethyl-5-*n*-propyl-uracil (X), described below, its melting point was strongly depressed.

Anal. Calcd. for $C_9H_{14}O_2N_2$: N, 15.38. Found: N, 15.76.

(B) Six-tenths gram of sodium was dissolved in 100 cc. of absolute alcohol, and then 2.1 g. of VI was dissolved in the alcoholate solution. To this cold solution, 2.5 cc. of dimethyl sulfate was then added slowly with frequent shaking. The mixture now was heated for two hours. After distilling off the excess alcohol, the residue was treated with water and extracted with benzene. The benzene solution was dried and solvent removed as usual, whereupon a solid residue was obtained. After crystallizing from benzene and petroleum ether, it melted at 193–194°. On mixing with IX described above, there was no lowering of the melting point.

The Molecular Rearrangement of 4-Methyl-5-*n*-propyl-2,6-dimethoxy-pyrimidine (III). (A) Rearrangement of (III) to (IV).—Two grams of III was heated in an oil-bath at 260–280° for three hours. At first, there was vigorous ebullition which gradually subsided and finally ceased as the proportion of the rearranged compound increased. On cooling, the brown colored reaction product completely solidified. It was dissolved in hot benzene, to which petroleum ether was added just to turbidity. On cooling, the rearranged product separated in needles. After recrystallization from a benzene–petroleum ether mixture, it melted at 74–75°. The yield was 1.8 g. or 90%.

Anal. Calcd. for $C_{10}H_{16}O_2N_2$: N, 14.28. Found: N, 14.21, 14.30.

(5) Chi and Chang, THIS JOURNAL, **60**, 1721 (1938).

(B) Rearrangement of (III) to (V).—Nine and eight-tenths grams of III was treated with 14.1 g. of freshly distilled methyl iodide. The mixture was then heated in a sealed tube at 50–60° for eight hours. After the tube was opened, the excess of methyl iodide was removed by a blast of air and the residue distilled under a vacuum. Compound V when pure boils at 180–182° under 4.5 mm. pressure and solidifies on slow cooling. The yield was quantitative. For analysis, it was recrystallized from petroleum ether, separating in needles.

Anal. Calcd. for $C_{10}H_{16}O_2N_2$: N, 14.28. Found: N, 14.16.

The structure of the compound was established by its behavior on hydrolysis, giving X.

Formation of X.—Compound V was heated with dilute hydrochloric acid for one hour. The solution was evaporated to dryness on a water-bath and the residue dissolved in hot water, whereupon X crystallized on cooling in colorless needles, melting at 148–150°.

Anal. Calcd. for $C_9H_{14}O_2N_2$: N, 15.38. Found: N, 15.50, 15.47.

(C) Rearrangement of the Partially Rearranged Pyrimidine (V) into the Completely Rearranged Pyrimidine (IV).—Five grams of V was heated at 330–350° for six to eight hours. The reaction mixture solidified on cooling. It dissolved in a little hot benzene, to which petroleum ether was added just to turbidity, whereupon (IV) separated in needles, melting at 74–75°. It proved to be identical with 1,3,4-trimethyl-5-*n*-propyluracil (IV) obtained by heating pyrimidine (III).

Anal. Calcd. for $C_{10}H_{16}O_2N_2$: N, 14.28. Found: N, 14.41, 14.55.

Summary

1. The action of phosphorus oxychloride on 4-methyl-5-*n*-propyluracil produces 4-methyl-5-*n*-propyl-2,6-dichloropyrimidine.

2. This 2,6-dichloropyrimidine reacts with sodium methylate and with sodium ethylate in a characteristic manner, giving the corresponding 2,6-dimethoxy-pyrimidine, and 2,6-diethoxy-pyrimidine derivatives, respectively.

3. 4-Methyl-5-*n*-propyl-2,6-dimethoxy-pyrimidine and 2-oxy-3,4-dimethyl-5-*n*-propyl-6-methoxy-pyrimidine can be rearranged to their isomeric and stable *lactam* modification, 1,3,4-trimethyl-5-*n*-propyluracil, on heating at an elevated temperature. On the other hand, 4-methyl-5-*n*-propyl-2,6-dimethoxy-pyrimidine rearranges only partially on heating with methyl iodide at 50–60° to 2-oxy-3,4-dimethyl-5-*n*-propyl-6-methoxy-pyrimidine.

WUCHOW, CHINA RECEIVED JULY 5, 1939

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

Oxidation of Glycosides by Means of Lead Tetraacetate in Aqueous Solution

BY J. M. GROSHEINTZ

In a previous paper[1] there was described a new technique for the application of lead tetraacetate as an oxidizing agent. It was shown that the cleavage of the carbon chain in compounds containing two and three adjacent hydroxyl groups could be carried out in aqueous solution as well as in non-aqueous solution. Lead tetraacetate therefore can replace periodic acid in most instances in which aqueous solvents are required.

E. L. Jackson and C. S. Hudson,[2] in their determination of ring structure and alpha- and beta-configuration of glycosides, thoroughly investigated the cleavage of the carbon chain of a number of glycosides by oxidation with periodic acid. In the present paper parallel experiments with lead tetraacetate are reported in order to show the similar action of this reagent on glycosides in aqueous solution.[3] Starting with the optical antipodes of two glycosides used by E. L. Jackson and C. S. Hudson[2] the oxidation products and their derivatives were compared with the products already known.

The oxidation of alpha- (I) and beta-methyl-*l*-arabinopyranosides with lead tetraacetate in water was shown to remove carbon atom 3 and form carbonyl groups at carbon atom 2 and 4, producing the two enantiomorphic forms of methoxy-diglycolic aldehyde[4] (II).

Contrary to previous experience,[1] *three* molecules of lead tetraacetate, instead of two, were required to complete this reaction. In seeking for

(1) Erich Baer, J. M. Grosheintz and H. O. L. Fischer, THIS JOURNAL, **61**, 2607 (1939).

(2) E. L. Jackson and C. S. Hudson, *ibid.*, **59**, 994 (1937).

(3) Compare also W. S. McClenahan and R. C. Hockett, *ibid.*, **60**, 2061 (1938).

(4) The oxidation products are named in accordance with E. L. Jackson and C. S. Hudson, *ibid.*, **59**, 994 (1937), as derivatives of diglycolic aldehyde. Prefixes D′ and L′ distinguish the configuration of carbon atom 1 in the products from the alpha- and beta-methyl-glycosides, L′ signifying the configuration of carbon atom 1 as in alpha-methyl-*l*-arabinopyranoside.