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## THE SYNTHESIS OF UREIDES OF CERTAIN MONOBASIC ACIDS AND KETONES.\*

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It is well known that certain ureides prepared from dibasic acids possess marked hypnotic action. In view of this fact it seemed of interest to prepare ureides from brominated aliphatic monobasic acids and ketones with a view to studying their physiological action.

The compounds prepared were:  $\alpha$ -bromo-*n*-caproyl ureide,  $\alpha$ -bromo-iso-caproyl ureide, methyl- $\beta$ - $\beta$ -dimethyl-2-urea  $\alpha$ - $\alpha$ -dibromo ethyl ketone and  $\beta$ - $\beta$ -dimethyl-2-urea- $\alpha$ - $\alpha$ -dibromo ethyl-iso-propyl ketone.

### EXPERIMENTAL.

*$\alpha$ -Bromo-Caproyl Ureide*  $C_7H_{13}O_2N_2Br$ .—Place a mixture of 56 Gm. of *n*-caproic acid and 3 Gm. of red phosphorus in a 500-cc. round-bottomed flask having a ground glass neck into which is fitted an upright condenser. To the mixture add 71 Gm. of bromine drop by drop and reflux over a water-bath until the contents assume a light yellow color. The brominated acid is separated from the mixture by distillation at reduced pressure. A total of 74 Gm. were obtained. The acid was light yellow in color, possessed a faint but persistent odor, insoluble in water, soluble in alcohol, ether and chloroform; boiling point  $131^\circ C.$  at 9 mm.;  $d_{23} 0.9404$ ;  $n_D^{20} 1.423$ ;  $[\alpha]_D^{25} -47.46^\circ$  in benzene.

To prepare the acyl chloride derivative an excess (10 Gm.) of thionyl chloride is added to the acid (20 Gm.) in a manner similar to that used in the bromination. Remove the sulfur dioxide by heating on the water-bath and separate the prepared acyl chloride derivative by distillation at reduced pressure. The pure compound (21 Gm.) possessed a boiling point of  $98^\circ C.$  at 30-mm. pressure.

The ureide is finally prepared by mixing the brominated acyl chloride (19 Gm.) with urea (18 Gm.) and slightly warmed on a water-bath. The mixture at first liquefies, after which it becomes a solid mass. The mass is neutralized by washing with several portions of aqueous sodium carbonate solution after which it is washed with distilled water.

After several recrystallizations from a hot 50 per cent solution of alcohol the ureide melted at  $175^\circ C.$  It consisted of colorless crystals having a slight but persistent taste, insoluble in water and fixed oils but soluble in 95 per cent alcohol, ether and chloroform.

A nitrogen determination showed the compound to contain 11.07 per cent N as compared to 11.45 per cent calculated on the basis of the formula  $C_7H_{13}O_2N_2Br$ .

*$\alpha$ -Bromo-iso-Caproyl Ureide*  $C_7H_{13}O_2N_2Br$ .—The method used in preparing the iso compound was essentially the same as that outlined for the normal compound. Starting with 60 Gm.

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of iso-caproic acid and 83 Gm. of bromine a yield of 30 Gm. of the brominated acid was obtained which possessed the following constants: Boiling point 130° C. at 25 mm.;  $d_{23}^{\circ}$  0.9923;  $n_D^{20}$  1.4426;  $[\alpha]_D^{25}$  -57.42° in benzene.

The acyl chloride was prepared by treating 25 Gm. of the brominated acid with 12 Gm. of the thionyl chloride as a result of which there was obtained 23 Gm. of the pure product having a boiling point of 83° C. at 20-mm. pressure. The liquid was light yellow in color, very irritating and somewhat unstable in air.

By using 21 Gm. of the brominated acyl chloride and 20 Gm. of urea the crystalline ureide melting at 161° C. was prepared. With the exception of the melting point its general properties were the same as the ureide prepared from the *n*-caproic acid. A nitrogen determination showed the product to contain 11.73 per cent nitrogen, while that calculated from the formula  $C_7H_{13}O_2N_2Br$  was 11.45 per cent.

*Methyl- $\beta$ - $\beta$ -Dimethyl-2-Urea- $\alpha$ - $\alpha$ -Dibromo Ethyl Ketone*  $C_7H_{12}O_2N_2Br_2$ .—Place 240 Gm. of commercial dimethyl-ketone in a Soxhlet extractor in the presence of barium hydroxide and reflux according to the method of Conant and Tuttle (1). Filter and heat on a water-bath to remove any excess ketone remaining and finally separate the diacetone alcohol by distillation at reduced pressure.

The alcohol possessed the following physical constants: Boiling point 81° C. at 25 mm.;  $d_{23}^{\circ}$  0.8741;  $n_D^{25}$  1.6560.

In the preparation of the dibromo-substituted product the method of Issotacherko (2) is employed whereby 68 Gm. of bromine are added, from a dropping funnel, to a mixture of 25 Gm. of the hydroxy ketone, 18 Gm. of calcium carbonate and 50 cc. of water. Wash the brominated compound with water and next extract with small portions of ether. Dry the combined ether washings with calcium chloride, filter and allow ether to evaporate spontaneously. Purification by distillation yielded a light yellow, viscous liquid boiling between 49° and 50° C. at 20 mm.

Chlorinate the dibromo-hydroxy-ketone by treating 15 Gm. with 9 Gm. of thionyl chloride. The purified product obtained by distillation at reduced pressure was a light yellow liquid which boiled at 47° C. at 29-mm. pressure.

Warm the dibromo-mono-chlor-ketone (9 Gm.) on a water-bath with 12 Gm. of urea. When complete solution has been effected the mixture is allowed to cool after which it solidifies into a solid mass of crystals. From hot secondary butyl alcohol the solid precipitated in form of colorless needles which melted at 145° C. They possessed a mild characteristic odor and salty taste, soluble in water, physiological saline solution and alcohol, but insoluble in ether and chloroform. Analysis of the compound showed 8.53 per cent nitrogen as compared to 8.37 per cent calculated from the formula  $C_7H_{12}O_2N_2Br_2$ .

*$\beta$ - $\beta$ -Dimethyl-2-Urea- $\alpha$ - $\alpha$ -Dibromo-Ethyl-iso-Propyl Ketone*  $C_9H_{16}O_2N_2Br_2$ .—This compound was prepared in the same manner as that outlined for the normal ketone. Starting with 60 Gm. of di-methyl ketone and 74 Gm. of methyl iso-propyl ketone there was obtained 18 Gm. of pure  $\beta$ , $\beta$ -dimethyl-2-hydroxy-ethyl-iso-propyl ketone. It was light yellow in color of characteristic odor and possessed the following physical constants: boiling point 86° C. at 25 mm.;  $d_{23}^{\circ}$  0.8727;  $n_D^{20}$  1.6623.

The mono-chlor substituted ketone was formed from 10 Gm. of the dibromohydroxy ketone and 7 Gm. of thionyl chloride. A total of 9 Gm. of the purified liquid product was obtained. It was light green in color and boiled at 104° C. at 20-mm. pressure.

The ureide was prepared from the mono-chlor derivative and urea. After repeated recrystallization from hot secondary butyl alcohol the crystals melted at 123° C. They were soluble in water and normal salt solution but insoluble in ether and chloroform. Analysis of the compound gave 8.01 per cent nitrogen, whereas the amount calculated from the formula  $C_9H_{16}O_2N_2Br_2$  was 8.37 per cent.

A preliminary study of the physiological properties of the compounds made by administering them to white rats, indicated that they possess hypnotic properties. Further detailed studies of their physiological action are being carried on. In addition the following new compounds are being prepared and their physiological action will be studied in detail:  $\alpha$ -bromo-secondary butyl acetyl ureide,

$\alpha$ -bromo-tertiary butyl acetyl ureide,  $\alpha$ -bromo-di-methyl ethyl acetyl ureide,  $\alpha$ -bromo-di-ethyl acetyl ureide,  $\alpha$ -bromo-methyl-iso-propyl acetyl ureide.

#### SUMMARY.

Four aliphatic ureides were prepared and their general properties determined. A preliminary study of their physiological action has indicated that they may be of value as sedatives or hypnotics.

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### A NOTE ON THE PRESENCE OF MALE SEX HORMONE IN FISH TESTES.\*

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The earliest knowledge of the comb growth activity of the testes was gained by A. Pezard in 1918 (1). The hormone activity was first extracted from bull testes in 1927 by L. C. McGee (2).

The history and literature is excellently reviewed by C. R. Moore in the *Journal of the American Medical Association* (3). It will be noticed that the active principle has been obtained from the bull, goat and ram testicles and human male urine, but its occurrence outside the mammalian family has not been studied.

With this in mind and in consideration of the fact that the testes of the Silver Salmon are very large and that great numbers of this fish are caught annually, this investigation was undertaken to determine the presence or absence of the hormone and the quantity.

The male salmon were taken during the breeding season from the state fish-traps at Goldbar, Washington. The testes were removed and frozen for storage during a period of one month. The method for extraction of the hormone was essentially that followed by Gallagher and Koch (4); 3100 Gm. of the tissue were ground and extracted with four volumes of 95% alcohol for five days. The alcohol was then expressed from the tissue and removed by distillation at 20-mm. pressure at 25° C. The solution was concentrated to a sludge of about 1500-cc. volume.

The sludge from above was extracted with benzene until all color was removed and evaporation of a benzene sample left no residue.

The benzene was removed by distillation at 40-mm. pressure at 18° C. A semi-solid mass of 125 cc. remained. The benzene was completely removed by a current of dry air, and the residue treated with acetone at -10° C. for 24 hours, then the acetone was filtered and removed by distillation at 70-mm. pressure at 18° C.

The residue so obtained weighed 12.047 Gm. and was assayed on capons by the method of Gallagher and Koch (5). We were, however, unable to obtain leghorn capons such as were used by the authors and used instead the larger barred rock capons. Previous work (6) has shown that heavier breeds of capons are much less reactive to the hormone than are the white or brown leghorn capons which have become standard birds for assay. We therefore regard the growth obtained in our birds as being positive. Although the growth obtained was not as large as would

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