SYNTHESIS OF β,γ-DIHYDROXY-PROPYL-GUANIDINE.

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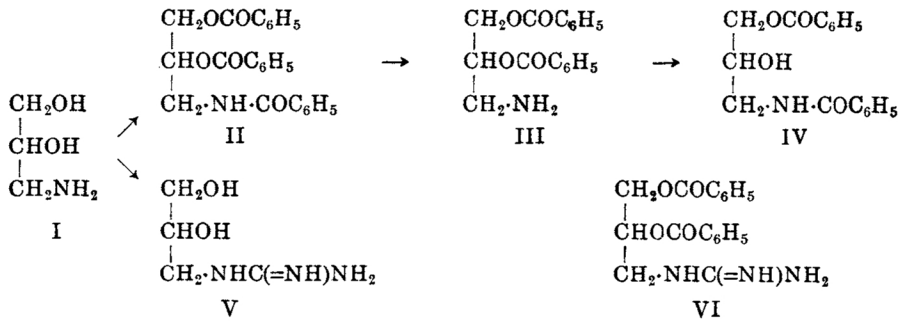
One of us (K.) has synthesized β-hydroxy-ethyl-guanidine[1]. Polyhydroxy-alkyl-guanidine, as we are aware, seems not yet been described in the literature. With the object of enlarging our knowledge upon the synthetic methods of polyhydroxy-alkyl-guanidine we attempted to synthesize β,γ-dihydroxy-propyl-guanidine, on which will be briefly reported here.

Starting from glycerol we first obtained amino-propylene glycol (I).

(1) S. Kawai, *Sci. Pap. Inst. Phys. Chem. Research, Japan*, **16** (1931), 24.



Amino-propylene glycol was benzoylated to its tribenzoyl-derivative (II) from which one benzoyl group was removed to *O,O'*-dibenzoyl-γ-amino-propylene glycol (III)[2]. *O,O'*-Dibenzoyl-γ-amino-propylene glycol hydrochloride (III) and an equivalent quantity of cyanamide were heated at 120–130°C in a sealed tube, absolute alcohol, or anhydrous pyridine being chosen as the solvents. In both cases, instead of procuring the expected β,γ-dibenzoyl-propyl-guanidine (VI), the reaction proceeded in an unexpected manner, and the sole crystalline product which we gained was the *O,N*-dibenzoyl-γ-amino-propylene glycol of Bergmann (IV)[3]. When we submitted *O*-methyl-pseudo-urea (free base) to reaction in place of cyanamide, the result was the same. In all cases the reactions ended in the acyl displacement from oxygen to nitrogen.

Our trial to synthesize β,γ-dihydroxy-propyl guanidine (V) succeeded, however, when we applied free amino-propylene glycol (I) and *S*-methyl-pseudo-thiourea hydroiodide as the starting materials. The β,γ-dihydroxy-propyl-guanidine (V) was isolated and identified as its picrate.

Experimental.

Amino-propylene glycol (I). Glycerol-α-monochlorhydrin was first synthesized after R. Adams[4], which was transformed into glycidol[5]. The latter was converted to amino-propylene glycol[6] (b.p. 163–165°/18 mm.) with concentrated aqueous ammonia.

O,N-dibenzoyl-γ-amino-propylene glycol (IV). Only one case will be written here for simplification. Into a sodium methylate solution (from 0.5 g. of metallic sodium and 5 c.c. of absolute methyl alcohol), which was cooled with ice water from outside, an absolute methyl alcoholic solution (10 c.c.) of *O*-methyl-pseudo-urea hydrochloride[7] (2.4 g.)

(2) M. Bergmann, *Ber.*, **54** (1921), 936.
(3) *Loc. cit.*
(4) R. Adams, "Organic Synthesis," II, 33.
(5) J.U. Nef, *Ann.*, **335** (1904), 231. T.H. Rider, *J. Am. Chem. Soc.*, **52** (1930), 1521.
(6) L. Knorr and E. Knorr, *Ber.*, **32** (1899), 752.
(7) J. Stieglitz, *Ber.*, **33** (1900), 1517.

was slowly added. After standing for about an hour, the separated sodium chloride was filtered off. Into this filtered solution *O,O'*-dibenzoyl-γ-amino-propylene glycol hydrochloride (III)[8] (7.28 g.) was added and the whole was shaken until dissolution was complete, temperature not being raised above 30°C.

After standing overnight the solution was concentrated to about two-thirds of its original volume under reduced pressure. Two days later the separated crystals were sucked off and were recrystallized several times from aqueous methyl alcohol. Colourless long plates, m.p. 108–109°C. Judging from its melting po nt and the analytical results no doubt can be inserted in its identity with the Bergmann's *O,N*-dibenzoyl-γ-amino-propylene glycol. Bergmann gives m.p. 109°C (corr.). (Found: C, 68.14, 67.99; H, 5.61, 5.69; N, 4.67, 4.50. Calc. for $C_{17}H_{17}O_4N$: C, 68.20; H, 5.73; N, 4.68%.)

β,γ-Dihydroxy-propyl-guanidine (V). Into an alcoholic solution (10 c.c.) of amino-propylene glycol (0.91 g., $^1/_{100}$ mol) *S*-methyl-pseudo-thiourea hydroiodide (2.18 g., $^1/_{100}$ mol) was added and the whole was refluxed on a steam bath for about 1.5 hours, strong evolution of mercaptan being observed. When the major part of the solvent was driven off under reduced pressure from the reaction mixture we obtained a syrupy mass, which showed no sign of crystallization even though it was kept in a vacuum desiccator for several days.

The syrup, however, exhibits positive colour-reactions of guanidine and it can be concluded that β,γ-dihydroxy-propyl guanidine hydroiodide was produced, in spite of its non-crystallizing tendency, which is presumably originated in its hygroscopic nature. The attempt to isolate the hydroiodide was then abandoned and the syrupy material was treated with a concentrated aqueous solution of sodium picrate (2.5 g.). Yellow crystals soon separated, which were collected. Yield 1.45 g. The picrate thus obtained was recrystallized several times from water. M.p. 126°C. Yellow fine prisms.

As is shown in the following analytical data, as well as the positive colour-reactions of guanidine (Sakaguchi's test, carmine red; Weber's test, blood red) it can be concluded that β,γ-dihydroxy-propyl-guanidine picrate was obtained. (Found: C,33.26, 33.55; H, 3.71, 4.04; N, 22.89, 22.83[9]. Calc. for $C_{10}H_{14}O_9N_6$: C, 33.13; H, 3.90; N, 23.20%.)

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(8) M. Bergmann, *loc. cit.*

(9) The nitrogen analysis of guanidine derivative, arginine for instance, often shows too small amount of nitrogen.