

## NOTE.

*Application of the Bischler-Napieralski Reaction to  $\delta$ -Ketoazelaodi- $\beta$ -veratrylethylamide.* By F. E. KING and ROBERT ROBINSON.

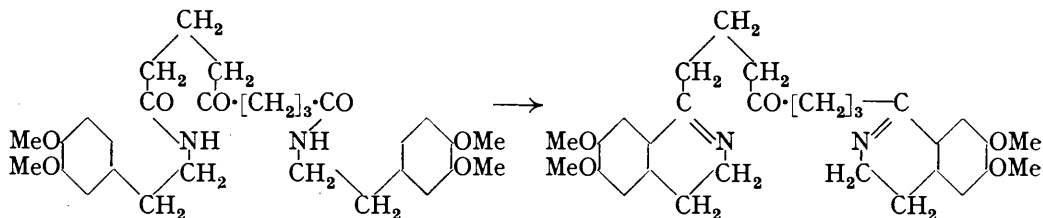
CHILD and PYMAN (J., 1929, 2010) prepared the di- $\beta$ -veratrylethylamides of the series of *n*-dibasic acids from oxalic acid to decane-1 : 10-dicarboxylic acid and cyclised a number of these amides to bisdihydroisoquinoline derivatives.

We proposed to adapt Child and Pyman's method by the use of dibasic acids substituted in the polymethylene chain in such a way as to render possible the eventual construction of a tricyclic nucleus.

The double ring closure of the *di- $\beta$ -veratrylethylamide* of  $\delta$ -ketoazelaic acid to a bisdihydroisoquinoline derivative has been studied in the hope of synthesising an analogue of emetine. The anticipated product, isolated as a picrate, was obtained in accordance with the scheme shown on p. 2120.

*Methyl  $\delta$ -Ketoazelate.*—The crude ketotetracarboxylic ester (50 g.), prepared by the method of v. Pechmann and Sidgwick (*Ber.*, 1904, **37**, 3816), was refluxed with a mixture of concentrated hydrochloric acid (100 g.) and water (100 g.) for 5 hours. The reddish solid obtained on

evaporation of the solution under diminished pressure was refluxed with methyl-alcoholic hydrogen chloride, and the ester isolated in the usual manner and distilled. The main fraction (25 g.), b. p. 185—195°/15 mm., solidified, and after recrystallisation from aqueous methyl alcohol gave methyl  $\delta$ -ketoazelaate in colourless, glistening leaflets, m. p. 34° (m. p. 30—31°, v. Pechmann and Sidgwick) (Found : C, 57.6; H, 7.9. Calc. for  $C_{11}H_{18}O_5$  : C, 57.4; H, 7.8%).



The ester (2.5 g.) was boiled with concentrated hydrochloric acid (3.5 c.c.) and water (12 c.c.) for 5 minutes, and the solution evaporated at 60° under diminished pressure, leaving a residue (2.1 g.), m. p. 106—108°. When recrystallised from ethyl acetate, this gave pure  $\delta$ -ketoazelaic acid in colourless prisms, m. p. 108—109° (Found : C, 53.3; H, 7.1. Calc. for  $C_9H_{14}O_5$  : C, 53.5; H, 6.9%). The isomeride, m. p. 101—102°, described by v. Pechmann and Sidgwick, does not appear to be formed under these conditions.

**$\delta$ -Ketoazelaodi- $\beta$ -veratrylethylamide.**—Methyl ketoazelaate (2.3 g.) was heated with 2 equivs. of  $\beta$ -veratrylethylamine (3.6 g.) for 2½ hours in an oil-bath at 170—180°, and the whole dissolved in alcohol containing ethyl acetate. The product (3.8 g.), m. p. 143—145°, obtained was recrystallised from the same solvents, giving the *diamide* as a mass of colourless fine prisms, m. p. 147°. The crystals sintered when suddenly heated to 135°, and satisfactory analyses were only obtained when the compound had been heated above 100° in a vacuum (Found : C, 66.1; H, 7.8; N, 5.5; MeO, 24.0.  $C_{29}H_{40}O_7N_2$  requires C, 65.9; H, 7.6; N, 5.3; 4MeO, 23.5%). The 2 : 4-dinitrophenylhydrazone separated from alcohol as a voluminous mass of deep yellow needles, m. p. 135—136° (Found in material dried at 100° : C, 59.5; H, 6.0; N, 11.5.  $C_{35}H_{44}O_{10}N_6$  requires C, 59.3; H, 6.2; N, 11.9%).

**Ring Closure of  $\delta$ -Ketoazelaodi- $\beta$ -veratrylethylamide.**—A suspension of ketoazelaodi- $\beta$ -veratrylethylamide (2 g.) in dry toluene (25 c.c.) was heated with phosphoryl chloride (4 c.c.) at 110°. After 30—40 minutes the toluene layer was decanted from the yellow viscous deposit, which was washed with light petroleum and then dissolved in water. The brownish semi-solid material liberated by alkali could not be crystallised, but on solution in the minimum amount of dilute hydrochloric acid and mixing with aqueous picric acid, a partly crystalline precipitate was obtained. This was collected and extracted with small amounts of hot alcohol, whereby after fractional crystallisation a small quantity of a picrate consisting of lemon-yellow needles, m. p. 112—113° (efferv.), was obtained (Found in material dried in a high vacuum at 100° : C, 57.4; H, 6.0; N, 10.2%). The less soluble residue was dissolved in boiling acetone, and after several days large deep yellow cubes (ca. 1 g.) separated. Recrystallisation from acetone gave the *monopicrate* of  $\gamma$ -bis-(6 : 7-dimethoxy-3 : 4-dihydroisoquinolyl)dibutyl ketone, m. p. 181—182° (Found in pulverised material dried at 110° : C, 58.1, 58.2; H, 5.6, 5.7; N, 10.0, 10.0.  $C_{29}H_{36}O_5N_2, C_6H_5O_7N_3$  requires C, 58.3; H, 5.4; N, 9.7%).—DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [Received, November 10th, 1938.]