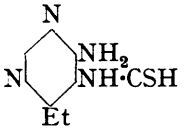
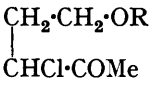
342. *Aneurin. Part III.* Methyl α-Chloro-γ-hydroxypropyl Ketone and its Application to Thiazole Synthesis.*

By A. R. Todd, F. Bergel, and (Miss) A. Jacob.

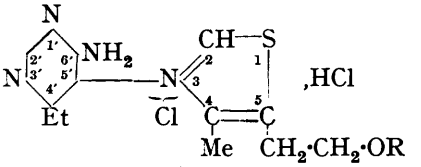
By cleavage of aneurin (vitamin B_1) with an acid solution of sodium sulphite Williams, Waterman, Keresztesy, and Buchman (*J. Amer. Chem. Soc.*, 1935, **57**, 536) obtained an acidic substance $C_6H_9O_3N_3S$, considered to be a pyrimidinesulphonic acid, and a base C_6H_9ONS, which Clarke and Gurin (*ibid.*, p. 1876) showed to be identical with 4-methyl-5-β-hydroxyethylthiazole. Largely on the basis of this work Williams (*ibid.*, p. 229) formulated the vitamin hydrochloride as 3-(6′-amino-4′-ethylpyrimidyl-5′)-4-methyl-5-β-hydroxyethylthiazolium chloride hydrochloride (III; R = H).



(I.)



(II.)



(III.)

It seemed possible that quaternary salts of type (III) might be synthesised by extending the methods employed for 3-arylthiazolium salts (Clarke and Gurin, *loc. cit.*; Todd, Bergel, and Karimullah, *Ber.*, 1936, **69**, 217) to the condensation of 6-amino-5-thioformamido-4-ethylpyrimidine (I) with a suitable α-halogenated ketone (II). In their synthesis of 4-methyl-5-β-hydroxyethylthiazole Clarke and Gurin (*loc. cit.*) condensed methyl α-chloro-γ-ethoxypropyl ketone (II; R = Et) with thioformamide and subsequently de-alkylated the 4-methyl-5-β-ethoxyethylthiazole initially formed, by heating in a sealed tube with concentrated hydrochloric acid. Such treatment is known to deaminate aneurin (Buchman and Williams, *J. Amer. Chem. Soc.*, 1935, **57**, 1751; Barger, Bergel, and Todd, *Ber.*, 1935, **68**, 2257), so the above-mentioned ethoxy-ketone was regarded as useless for our purpose.

We therefore synthesised *methyl α-chloro-γ-hydroxypropyl ketone* (II; R = H) according to the scheme:

$$CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2Br + CH_3{\cdot}CO{\cdot}CHNa{\cdot}CO_2Et \longrightarrow CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}CO{\cdot}CH_3 \quad \text{(IV.)}$$

$$\xrightarrow{SO_2Cl_2} CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CCl(CO_2Et){\cdot}CO{\cdot}CH_3 \quad \text{(V.)} \xrightarrow{\text{dil. } H_2SO_4} HO{\cdot}CH_2{\cdot}CH_2{\cdot}CHCl{\cdot}CO{\cdot}CH_3$$

The condensation of β-bromoethyl acetate with ethyl sodioacetoacetate at 160° (Haller and March, *Compt. rend.*, 1908, **139**, 100; *Bull. Soc. chim.*, 1905, **33**, 618) is unsatisfactory; better results are obtained by using benzene as a diluent and refluxing the mixture on the water-bath. Chlorination of (IV) with sulphuryl chloride proceeds smoothly, and the desired chloro-ketone is obtained on careful hydrolysis of the product (V).

Methyl α-chloro-γ-hydroxypropyl ketone condensed readily with thioformamide, yielding 4-methyl-5-β-hydroxyethylthiazole, whose *picrate* gave no depression in m. p. when mixed with the specimen (m. p. 162°) prepared from the vitamin.

Efforts were also made to prepare methyl α-halogeno-γ-phenoxypropyl ketones in the hope that the phenoxythiazoles resulting from their condensation with thioamides would yield the corresponding hydroxy-compounds under relatively mild conditions. At first, direct halogenation of methyl γ-phenoxypropyl ketone (Boyd, Barrett, and Robinson, J., 1932, 318) was tried under a variety of conditions, but no homogeneous products could be isolated. The synthesis of *methyl α-chloro-γ-phenoxypropyl ketone* (II; R = Ph) was, however, effected by a method analogous to that employed for the corresponding hydroxy-compound (II; R = H); as is evident from the chlorine content, the substance could

* Part II; *Ber.*, 1936, **69**, 217.

not be purified completely, but condensation with thioacetamide gave in good yield, 2 : 4-dimethyl-5-β-phenoxyethylthiazole, isolated as its *picrate*. Further experiments with phenoxythiazoles were discontinued, as replacement of the phenoxy-group by hydroxyl could not be satisfactorily accomplished.

Experimental.

Ethyl α-2-Acetoxyethylacetoacetate (IV).—To a suspension of dry ethyl sodioacetoacetate (152 g.) in dry benzene (700 c.c.), β-bromoethyl acetate (167 g.) was added at 15—20°. The mixture was heated on the water-bath until the solution reacted faintly alkaline (6—10 hours), then cooled, poured into ice-water, and extracted with ether. After removal of the ether the residual oil was distilled under reduced pressure, the fraction, b. p. 138—142°/12 mm., being collected (yield, 25%). Haller and March (*loc. cit.*) give b. p. 147—150°/13 mm.

Ethyl α-Chloro-α-2-acetoxyethylacetoacetate (V).—Sulphuryl chloride (82 g.) was added during 1 hour with stirring to the ester (IV) (123 g.) at 0°. The solution was kept at 0° for a further hour, then diluted with ether (250 c.c.) and refluxed for a short time to remove sulphur dioxide and hydrogen chloride. The ether was removed, and the residual oil repeatedly fractionated in a vacuum. The main fraction, b. p. 120—121°/2 mm., was collected (yield, 86%) (Found : C, 47·9; H, 6·0; Cl, 13·3. $C_{10}H_{15}O_5Cl$ requires C, 47·9; H, 6·0; Cl, 14·1%).

Methyl α-Chloro-γ-acetoxypropyl Ketone (II; R = $CO{\cdot}CH_3$).—The above ester (V) was heated under reflux for 6 hours with a mixture of dilute sulphuric acid (20 c.c. of 15%) and glacial acetic acid (20 c.c.). The solution was cooled, poured into water, and extracted with ether. After removal of the ether and acetic acid a colourless liquid was obtained which after several fractionations boiled at 90—93/2 mm. (yield, 40%) (Found : C, 47·1; H, 6·2; Cl, 19·8. $C_7H_{11}O_3Cl$ requires C, 47·0; H, 6·2; Cl, 19·9%).

Methyl α-Chloro-γ-hydroxypropyl Ketone (II; R = H).—The chloro-ester (V) was heated under reflux during 4 hours with dilute sulphuric acid (35 c.c. of 35%) and alcohol (70 c.c.), then poured into water, and the mixture extracted with ether. On removal of ether from the dried extract an oil was left which after repeated fractionation gave a colourless liquid, b. p. 85—92°/16 mm. (yield, 20%) (Found : Cl, 25·4. $C_5H_9O_2Cl$ requires Cl, 26·0%).

4-Methyl-5-β-hydroxyethylthiazole.—An ethereal solution of thioformamide was prepared by shaking together finely powdered phosphorus pentasulphide (12 g.), formamide (20 g.), and absolute ether (200 c.c.) for *ca.* 20 hours (Gabriel, *Ber.*, 1916, **49**, 1145); the clear ethereal layer was decanted and used as a stock solution of thioformamide.

When a mixture of the chloro-ketone (II; R = H) (250 mg.) and the thioformamide solution (10 c.c.) was kept, colourless crystals of the thiazole hydrochloride slowly separated. After 5 hours the ether was distilled off, and the residue heated for 1 hour at 100°, cooled, and dissolved in dilute hydrochloric acid. After extraction with ether to remove any unchanged ketone, the solution was made strongly alkaline and again extracted with ether. The extract on evaporation yielded 4-methyl-5-β-hydroxyethylthiazole as an almost colourless oil, b. p. 250—255° (capillary method of Emich). The base was not purified further; treatment with ethereal picric acid gave a *picrate* crystallising from alcohol in yellow needles, m. p. 162—163° (Found : S, 8·2. $C_{12}H_{12}O_8N_4S$ requires S, 8·6%).

Ethyl α-2-Phenoxyethylacetoacetate.—This *ester* was prepared from β-phenoxyethyl bromide and ethyl sodioacetoacetate in alcoholic solution (cf. Boyd, Barrett, and Robinson, *loc. cit.*). It had b. p. 148°/4 mm. (Found : C, 68·1; H, 7·3. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

Ethyl α-Chloro-α-2-phenoxyethylacetoacetate.—The above ester (10 g.) was chlorinated with sulphuryl chloride (6 g.) in the manner described under the corresponding acetoxy-compound (V). The *product* was a colourless liquid, b. p. 135—140°/3 mm. (yield, 70%) (Found : C, 59·3; H, 6·1; Cl, 11·9. $C_{14}H_{17}O_4Cl$ requires C, 59·1; H, 6·0; Cl, 12·4%).

Methyl α-Chloro-γ-phenoxypropyl Ketone (II; R = Ph).—The above chloro-ester (7 g.) was hydrolysed by refluxing for 4 hours with a mixture of dilute sulphuric acid (14 c.c. of 15%) and glacial acetic acid (14 c.c.). After repeated distillation the main fraction of the product boiled at 168—172°/12 mm. (Found : C, 62·0; H, 6·0; Cl, 12·2. $C_{11}H_{13}O_2Cl$ requires C, 62·1; H, 6·1; Cl, 16·7%). The low chlorine content may be due to partial decomposition during distillation; that the substance is mainly the desired ketone is shown by its condensation with thioacetamide.

2 : 4-Dimethyl-5-β-phenoxyethylthiazole.—The above chloro-ketone (200 mg.) reacted rapidly with thioacetamide (60 mg.) when the mixture was warmed for a few minutes over a free flame. The free base was finally obtained as a colourless thick oil. It gave a *picrate* crystal-

lising from alcohol in yellow needles, m. p. 122° (Found: N, 12·1; S, 6·8. $C_{19}H_{18}O_8N_4S$ requires N, 12·1; S, 6·9%).

The authors express their thanks to the Rockefeller Foundation for a grant, and to the Beit Memorial Trustees for a Fellowship awarded to one of them (A. R. T.).

MEDICAL CHEMISTRY DEPARTMENT, UNIVERSITY OF EDINBURGH. [*Received, August 15th*, 1936.]