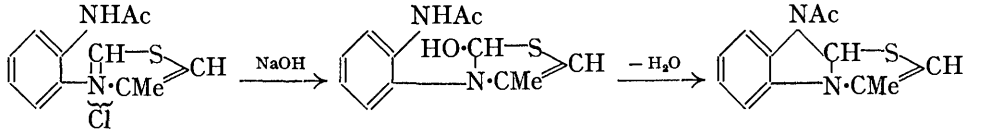
197. *Substituted Phenyl- and Benzyl-thiazolium Salts.*

By KARIMULLAH.

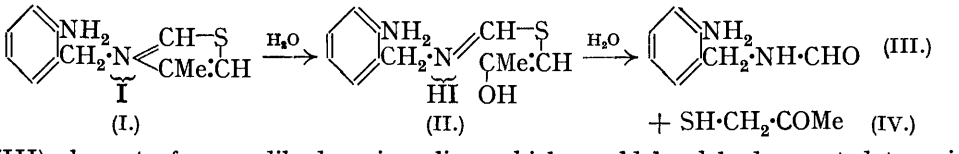
IN the course of experiments on the synthesis of aneurin, attempts were made to prepare a substance having a constitution like that originally proposed for this vitamin by Williams (*J. Amer. Chem. Soc.*, 1935, **57**, 229), but having a phenyl instead of a pyrimidine nucleus. Such an analogue would be *N*-*o*-aminophenylthiazolium chloride, for which monothioformyl-*o*-phenylenediamine could serve as a point of departure. The latter substance could, however, not be prepared because the thioformylation of *o*-phenylenediamine leads to benzimidazole (Todd, Bergel, Karimullah, and Keller, this vol., p. **361**). Therefore monoacetyl-*o*-phenylenediamine was thioformylated and then condensed with chloroacetone, to form a thiazolium chloride. Attempts to deacetylate the product with sodium hydroxide and subsequent treatment in ether with hydrogen chloride gave a crystalline salt of a tertiary base isomeric with the original substance. The new salt may be a dihydrothiazole hydrochloride and it might be formed according to the following scheme :



On oxidation with potassium ferricyanide in alkaline solution, no fluorescence was observed.

After the present formula for aneurin had been put forward and confirmed by synthesis (Williams and Cline, *J. Amer. Chem. Soc.*, 1936, **58**, 1504; Todd and Bergel, this vol., p. **364**) similar experiments were made with a view to obtaining *N*-*o*-aminobenzylthiazolium chloride. *o*-Aminobenzylamine on thioformylation yields dihydroquinazoline in quantitative yield (Todd, Bergel, Karimullah, and Keller, *loc. cit.*). The hydrochloride of *o*-aminobenzyl chloride, on treatment with 4-methylthiazole, merely yielded the highly polymerised product $\left(C_6H_4<\begin{matrix}NH\\CH_2\end{matrix}\right)_n$ recorded by Gabriel and Posner (*Ber.*, 1894, **27**, 3514). Hence reduction of N-o-*nitrobenzyl*-4-*methylthiazolium chloride* was resorted to, hydriodic acid and red phosphorus being found to be the most suitable agent. The *iodide* formed, being rather unstable, was converted into the corresponding *chloride*. On alkaline oxidation with potassium ferricyanide, this compound gave a blue fluorescence in ultraviolet light, but a crystalline substance like thiochrome could not be separated.

Alkaline oxidation of this iodide with potassium ferricyanide invariably gave iodoform, and when the same operation was repeated with other *N*-phenyl- or -benzyl-thiazolium iodides, a very strong smell of *iso*nitrile was detected. This could be explained as follows :



(III) closes to form a dihydroquinazoline, which would be dehydrogenated to quinazoline, and (IV) gives iodoform with iodine set free from sodium iodide by potassium ferricyanide during the reaction. In the case of other *N*-phenylthiazolium iodides having no *o*-amino-group, the formyl group is further hydrolysed, giving a primary amine, which reacts with iodoform in an alkaline medium to form the *iso*nitrile.

Thiochrome could not be obtained quantitatively by oxidation of aneurin (compare Barger, Bergel, and Todd, *Ber.*, 1935, **68**, 2257), the yield being at the most 70%. It is suggested that a side reaction as stated above might lead to destruction of a good deal of aneurin.

Attempts to prepare a phenyl analogue of thiochrome by condensing *o*-chlorobenzyl chloride with 2-amino-4-methylthiazole according to Todd, Bergel, Fraenkel-Conrat, and Jacob (J., 1936, 1601) were without success. Presumably the chloromethyl group

reacts preferentially with the amino-group of the thiazole; moreover the chlorine in a benzene ring would be less reactive than when attached to the 6-position of a pyrimidine ring.

Experimental.

N-o-*Acetamidophenyl-4-methylthiazolium Chloride.*—Monoacetyl-*o*-phenylenediamine was prepared according to Leuchs (*Ber.*, 1907, **40**, 1084), but the tin was removed by hydrogen sulphide. Yield, 58%.

Thioformylmonoacetyl-*o*-phenylenediamine (5 g.) was dissolved in acetone (300 c.c.) by heating and, after cooling, chloroacetone (5 c.c.) was added. The mixture was kept overnight at room temperature and subsequently refluxed for 2 hours, and the acetone evaporated. The residue, after digestion with ether to remove unchanged material, crystallised from methanol–acetone (charcoal) in colourless plates, m. p. 222°. Yield, about 85% (Found : C, 53·8; H, 4·9; S, 11·5. $C_{12}H_{13}ON_2ClS$ requires C, 53·6; H, 4·8; S, 11·9%).

In all these condensations acetone proved to be a useful solvent. In alcoholic solution the thioformyl group was often hydrolysed and 2-methylbenzimidazole was obtained instead of a thiazolium salt. The *hydrochloride* of the tertiary base got by treatment with dilute sodium hydroxide solution had m. p. 188° (Found : C, 54·1; H, 4·9; S, 11·4; Cl, 13·4. $C_{12}H_{12}ON_2S,HCl$ requires C, 53·6; H, 4·8; S, 11·9; Cl, 13·2%).

N-o-Tolyl-4-methylthiazolium chloride, prepared as above from thioformo-*o*-toluidide (1 g.) and chloroacetone (1·2 g.) in acetone (30 c.c.), was converted by potassium iodide into the *iodide*, m. p. 230° (decomp.) after crystallisation from alcohol–ether. Yield, 90% (Found : C, 42·1; H, 4·1; S, 9·6. $C_{11}H_{12}NIS$ requires C, 41·7; H, 3·8; S, 10·0%).

N-*Benzyl-4-methylthiazolium Chloride.*—Thioformylbenzylamine, condensed with chloroacetone in equivalent amount in the usual manner, gave a *chloride* which showed no depression in m. p. when mixed with that obtained from benzyl chloride and 4-methylthiazole; m. p. 188° (Found : N, 6·1. $C_{11}H_{12}NClS$ requires N, 6·2%).

Similarly, N-o-*nitrobenzyl-4-methylthiazolium chloride* obtained from thioformyl-*o*-nitrobenzylamine and chloroacetone was identical with that from *o*-nitrobenzyl chloride and 4-methylthiazole; m. p. 200° (Found : N, 10·0. $C_{11}H_{11}O_2N_2ClS$ requires N, 10·3%).

N-o-*Chlorobenzyl-4-methylthiazolium Chloride.*—*o*-Chlorobenzyl chloride (3·5 g.) was heated with 4-methylthiazole (2·5 g.) on a water-bath for 2 hours. The crystalline mass was washed with ether and recrystallised from alcohol–ether; m. p. 190° (decomp.). Yield, 4 g. (Found : C, 50·3; H, 4·5; Cl, 26·8. $C_{11}H_{11}NCl_2S$ requires C, 50·7; H, 4·2; Cl, 27·3%).

2-o-*Chlorobenzylamino-4-methylthiazole hydrochloride*, prepared from *o*-chlorobenzyl chloride and 2-amino-4-methylthiazole as above, crystallised from ethyl alcohol–ether in colourless needles, m. p. 260° (decomp.) (Found : C, 48·4; H, 4·5; Cl, 25·5. $C_{11}H_{11}N_2ClS,HCl$ requires C, 48·0; H, 4·4; Cl, 25·8%). The free base melted at 100°. The hydrochloride and the free base showed bluish-violet fluorescence in ultra-violet light.

2-o-*Chlorobenzylaminothiazole hydrochloride*, prepared from *o*-chlorobenzyl chloride and 2-aminothiazole, had m. p. 245° (Found : C, 46·3; H, 3·9. $C_{10}H_9N_2ClS,HCl$ requires C, 46·0; H, 3·8%). The free base had m. p. 58°.

N-o-*Aminobenzyl-4-methylthiazolium Chloride Hydrochloride.*—Hydriodic acid (*d* 1·7; 8 c.c.) and red phosphorus (0·5 g.) were heated nearly to boiling. After removal of the flame *N-o*-nitrobenzyl-4-methylthiazolium chloride (1·5 g.) was added in portions. On each addition a slight reaction ensued. The whole was boiled for ½ hour. After cooling, the crystalline mass was collected on fritted glass filter and recrystallised from water containing a little hydriodic acid; m. p. 237° (decomp.). The crystals assumed a brownish-yellow colour on exposure to light. The *salt* was readily hydrolysed and each successive recrystallisation lowered the m. p. and the iodine content (Found : I, 54·6. $C_{11}H_{14}N_2I_2S$ requires I, 55·2%).

The *chloride* was found to be more stable and was prepared by shaking the iodide with freshly precipitated silver chloride in methanol for 4 hours. The filtrate was treated with excess of dry ether; the chloride crystalled in colourless needles, m. p. 213° (decomp.) (Found : N, 9·9; Cl, 25·7. $C_{11}H_{14}N_2Cl_2S$ requires N, 10·1; Cl, 25·7%).

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