(Tapazol). 4(5)-Methyl-2-thiocyanoimidazole was considerably less effective although exhibiting definite antithyroid activity.

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Synthesis of 5-Hydroxykynurenine[1]

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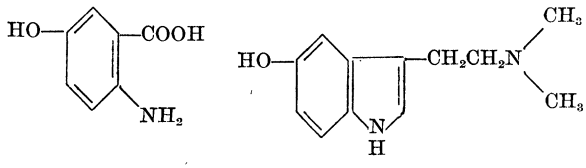
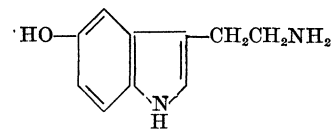
Kotake (*1*) isolated 5-hydroxyanthranilic acid (I) from the urine of rabbits injected with anthranilic acid. This fact and the isolation of the 5-hydroxytryptophan metabolites bufotenine (*2*) (II) and serotonine (*3*) (III) from the natural sources suggested the synthesis of 5-hydroxykynurenine (IV).

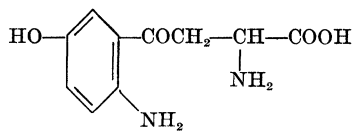


I

II



III



IV

The synthesis was performed as follows. 6-Nitro-3-methoxybenzoic acid was converted to its chloride by warming slightly with thionyl chloride. The resultant chloride (m.p. 34°) was condensed in dry chlorobenzene with the magnesium diethyl malonate and then decomposed to 6-nitro-3-methoxyacetophenone (m.p. 67° found : C 55.07, H 5.44, N 6.79; calc. for $C_9H_9O_4N$: C 55.4, H 4.7, N 7.19%) by warming with hydrochloric acid and acetic acid. This was then converted to 6-nitro-3-methoxy-ω-bromoacetophenone (m.p. 90° found : C 39.43, H 3.19, N 4.72; calc. for $C_9H_8O_4NBr$: C 39.42, H 2.92, N 5.11%) and then condensed with ethyl acetaminomalonate in the presence of sodium in absolute alcohol. The resultant ethyl acetamino-6-nitro-3-methoxyphenacyl malonate (m.p. 145° found : C 53.21, H 5.69, N 6.8; calc. for $C_{18}H_{22}O_9N_2$: C 52.7, H 5.4, N 6.83%) was decomposed by refluxing with hydrochloric acid and acetic acid to 6-nitro-3-methoxyphenacyl glycine hydrochloide (m.p. 199°) which gave with ninhydrin a yellow color.

This nitro amino acid was dissolved in diluted sulfuric acid and hydrogenated in the presence of palladium black. The 5-methoxykynurenine sulfate thus obtained melted at 191° with decomposition and showed with ninhydrin a reddish purple color. On paper chromatogram developed with butanol-acetic acid-water system it separated in two spots with Rf 0.32 and Rf 0.36 which presumably correspond to D and L isomers.

5-Hydroxykynurenine sulfate was obtained by refluxing methoxykynurenine sulfate with hydrobromic acid in an atmosphere of carbon dioxide. 5-Hydroxykynurenine sulfate (found : C 37.28, H 4.26, N 8.35; calc. for $C_{10}H_{14}O_8N_2S$: C 37.27, H 4.38, N 8.69%) was a colorless small prismatic needle and began to darken at 225° and carbonized completely at 255°. Its aqueous solution showed a marked green fluorescence and gave with ninhydrin a purple color, with diazotized sulfanilic acid a purple color, with dimethylaminobenzaldehyde in hydrochloric acid an orange color, with ferric chloride a brown color and decolorized chameleon solution. Its Rf value was 0.24 on the paper chromatogram developed with the supernatant of the mixture of acetic acid, butanol, and water in ratio 1 : 4 : 5. Its ultraviolet absorption spectra had a maximum at 405 mμ at pH 11.4 and a maximum at 378 mμ at pH 4.8.

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[2] We wish to express our thanks to the Takeda Research Laboratory for making elementary analyses.

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