A SYNTHESIS OF TRYPTOPHOL.

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(Received for publication, June 30, 1930.)

Felix Ehrlich demonstrated that yeast attacks the natural amino acids essentially by splitting off carbon dioxide and replacing the amino group with hydroxyl. By this reaction, the greater part of fusel oil is derived from the leucines. In the case of tryptophane, the process gives rise to tryptophol or 3-indole ethyl alcohol, first described by Ehrlich in 1912. Since then, the substance has engaged the attention of various investigators of intermediary metabolism (*cf.* Guggenheim and Löffler, 1915–16; Ward, 1923; Jackson, 1929). Notwithstanding this background of biological interest, there appears to be no recorded synthesis of tryptophol. It seemed worth while, therefore, to attempt such a synthesis with the object both of producing the substance itself and of extending the somewhat limited procedures available for the construction of compounds in the indole series. The writer has succeeded in securing tryptophol in a good yield and in a high state of purity through the reduction of indole acetic acid ester by means of sodium in alcohol. The properties of the synthetic product show that it is identical with the tryptophol prepared by the yeast decomposition of tryptophane according to the directions of Ehrlich.

EXPERIMENTAL.

Indole Acetic Acid.—This compound was prepared in good yield according to Majima and Hoshino (1925). Indole magnesium iodide was treated with chloroacetonitrile to produce 3-indole acetonitrile which on hydrolysis gave the 3-indole acetic acid. After purification it melted at 164–165° (corrected).

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Methyl and Ethyl Esters.—Both esters were readily secured in practically a quantitative yield in the usual way by refluxing the acid with a considerable excess of the proper absolute alcohol containing a little dry hydrochloric acid gas, followed by evaporation of the alcohol, washing of the ether solution of the ester with sodium bicarbonate solution and with water, drying of the ether solution with calcium chloride, and finally, vacuum distillation. Both esters distilled in the neighborhood of 180° at 2 mm. of pressure. Neither ester could be induced to crystallize.

Reduction of the Ester. Experiment 1.—8.5 gm. (0.045 mol) of the methyl ester were reduced in methyl alcohol (dried with sodium) with the proportions of solvent, sodium, and toluene and the use of mechanical stirrer as directed by Marvel and Tannenbaum (1922). The yield of crude product, which did not crystallize, amounted to 3.0 gm. (0.019 mol). This was converted to the picrate which was recrystallized from hot water and then subjected to alkaline decomposition and ether extraction. The evaporated ether extract was crystallized from dilute alcohol and then from ether-petroleum ether. The pure white crystals melted at 58° (corrected) and exhibited no melting point depression when mixed with a specimen of tryptophol prepared from tryptophane according to Ehrlich's method.

Experiment 2.—It was subsequently learned[1] that very good yields of certain dihydric alcohols could be obtained by simply adding very dry alcoholic solutions of the esters to the sodium. The experiment described below was performed in similar fashion. Commercial absolute ethyl alcohol was treated (*cf.* Smith, 1927) with sodium sufficient to react with all the water present and then in addition with enough ethyl phthalate to react with all the free alkali remaining in the solution. The alcohol was refluxed ½ hour and then distilled, to the amount of 250 cc., directly into the flask in which the reduction was to be carried out. To this alcohol, 9.15 gm. (0.045 mol) of dry ethyl indole acetate were next added, followed by 15 gm. (0.65 mol) of sodium. The flask was attached

[1] Private communication from Dr. Wallace H. Carothers of the Experimental Station of E. I. du Pont de Nemours and Company. Dr. R. H. F. Manske of Yale University has confirmed Dr. Carothers in this finding, and further has found ethyl phthalate a good inexpensive ester to use in preparing the alcohol according to the method of Smith (1927).

to a reflux condenser equipped with a calcium chloride tube, and after ½ hour, heated for 2 hours on the steam bath. A little remaining sodium was dissipated by the addition of a small amount of 50 per cent alcohol and the product worked up in the customary fashion. Direct crystallization from benzene-petroleum ether yielded 4.33 gm., melting at 57° (corrected) and 1.30 gm. melting

TABLE I.

Properties of Tryptophol and Derivatives.

Tryptophol sample.	M.p.	M.p. of picrate.	M.p. of phenyl urethane.	Nitrogen.
	°C.	°C.	°C.	*per cent*
(*a*) Ehrlich	59*	94–96†		9.02 (Dumas.)
(*b*) From tryptophane according to Ehrlich (*cf.* Jackson, 1929)	58–59‡	100–101§	130–131§	8.62 (Kjeldahl.)
(*c*) Synthetic (Experiment 2)	58–59‖	100–101§	130–131§	8.61 (")
(*d*) Mixed melting points, (*b*) and (*c*)	58–59	100–101	130–131	8.69 (Theory.)

All melting points are corrected.
The solvents employed are indicated by symbols:
* Ether-petroleum ether.
† Water.
‡ Dilute alcohol.
§ Benzene.
‖ Benzene-petroleum ether.

at 54–57° (corrected). An additional 0.25 gm. was obtained as the picrate. The total of 5.88 gm. amounts to a yield of 81 per cent of the theoretical. If the 0.70 gm. of indole acetic acid recovered is taken into consideration, the yield is 89 per cent of the theoretical. The product was purified by vacuum distillation and crystallization from benzene-petroleum ether to give beautiful white glistening plates. As an aid to comparison, the physical properties of various specimens of tryptophol and its derivatives are given in Table I.

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