THE ERGOT ALKALOIDS

XVII. THE DIMETHYLINDOLE FROM DIHYDROLYSERGIC ACID

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(Received for publication, March 13, 1939)

Among the volatile products formed on fusion of dihydrolysergic acid (1) an indole fraction was obtained from which a picrate was isolated in very small amount which melted at 148–150°. The analytical figures obtained with it approximated those of the picrate of an indole $C_{11}H_{13}N$. The indole still gave the dimethylaminobenzaldehyde test and therefore presumably had the α (or β) position still free (2). It was not identical with a β-*n*-propylindole. Since it was formed in such small amounts and was very difficult to purify, we have turned again more recently to the previously reported indole acid contained in the non-volatile alkali melt, which was also formed in very small amount (1).

This indole acid fraction was again prepared and subjected to low pressure distillation during which decarboxylation occurred. The resulting indole after recrystallization was finally obtained in very small yield with a melting point of 115–117°. A picrate prepared from one of the fractions melted at 185–187°. Since there was not sufficient of either the indole itself or its picrate with these melting points for analysis, analyses were obtained with several picrate fractions of somewhat lower melting points (175–183° and 164–168°). These analyses were in fair agreement with the figures required by a dimethylindole. Since the indole still gave the dimethylaminobenzaldehyde reaction, it appeared probable that it could be a 3,4-dimethylindole resulting by decarboxylation of a 4-methylindole-3-acetic acid. This would be expected as a scission product from the structure which we have derived for lysergic acid.

As a check on this conclusion the indoles were prepared from *m*-tolylhydrazine and propionaldehyde. Mendlik and Wibaut (3) had previously attempted the same synthesis and obtained but one substance (m.p. 116–117° and picrate m.p. 179–180°) which they concluded to be 3,6-dimethylindole. However, we have obtained two isomers, as would be expected,[1] one which must be *3,4-dimethylindole* and the other *3,6-dimethylindole.* The identity of these has not been directly established except by inference from the comparison with the above indole from lysergic acid. One of these, which melted at 117–118°, gave a picrate melting at 182–183° and was thus identical with that described by Mendlik and Wibaut. Neither this indole nor its picrate gave a depression with the substances obtained from lysergic acid and agreed in other properties with these substances. It may therefore be inferred that this substance is 3,4-dimethylindole and not the 3,6 derivative. The formation of a 3,6 derivative, barring unlikely rearrangements, is incompatible with the structure that we have derived for lysergic acid and which is at the same time a derivative of naphthalene, quinoline, and indole. The second synthetic indole which melted at 90–93° and gave a picrate melting at 163–164° would therefore be 3,6-dimethylindole.

The attempt will be made, when opportunity presents, to confirm this by the synthesis of 3,4-dimethylindole by another method.

EXPERIMENTAL

3,4- and 3,6-Dimethylindoles—5 gm. of propionaldehyde were treated with 10.4 gm. of *m*-tolylhydrazine and warmed. The hydrazone was extracted with ether and the solution was dried over K_2CO_3. After concentration the residue was treated with 30 gm. of anhydrous zinc chloride and the mixture was heated in an oil bath raised to 165°. When the reaction was completed, the contents of the flask were washed out with ether and excess 10 per cent HCl. The washed and dried ether extract was concentrated in an apparatus for sublimation of the residue. All the material subliming up to an oil bath temperature of 125° and under 0.2 mm. pressure was collected and the residue discarded. The sublimate which weighed about 3 gm. was dissolved in 30 cc. of

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[1] The formation of two isomeric oxindoles from the *m*-tolylhydrazide of propionic acid has already been reported (4).

warm petroleum ether. When chilled to −15°, crystallization began. The crystals were filtered off without washing and the filtrate was set aside to be treated as described below.

The crystalline fraction after repeated crystallization from petroleum ether formed flat needles which melted at 117–118°.

$C_{10}H_{11}N$. Calculated, C 82.76, H 7.64; found, C 82.89, H 7.69

This indole yielded a picrate from ethyl alcohol forming dark red needles which melted at 182–183°.

$C_{16}H_{14}O_7N_4$. Calculated, C 51.34, H 3.74; found, C 51.37, H 3.78

The above petroleum ether filtrate from the crystalline indole was concentrated and transferred to a 22 cm. microfractionating column. Fractionation was carried out under approximately 0.2 mm. pressure. Five fractions were collected. Each fraction was about 0.15 gm. with the exception of the second which weighed 0.33 gm.

The second fraction completely solidified on the condenser and showed a melting point of 60–90°. When dissolved in 3 cc. of petroleum ether and chilled to −15°, crystallization began. 0.28 gm. of broad, thin leaflets was collected, which melted at 90–93°.

0.1 gm. was converted to the picrate in 3 cc. of ethyl alcohol. 0.175 gm. of needles was collected which melted at 163–164°.

$C_{16}H_{14}O_7N_4$. Calculated, C 51.34, H 3.74; found, C 51.45, H 3.97

The indole recovered from the picrate after redistillation melted at 90–92°.

$C_{10}H_{11}N$. Calculated, C 82.76, H 7.64; found, C 82.97, H 7.65

Dimethylindole from Dihydrolysergic Acid—1.2 gm. of dihydrolysergic acid were ground with 7 gm. of KOH and placed in a fusion apparatus as previously described (1). The salt bath for heating the mixture was held at 300° for 0.5 hour.

The volatile material from the reaction was worked up in the manner previously given and 10 mg. of the indole fraction were obtained. Since this proved difficult to purify further, attention was turned to the alkali melt.

This melt was dissolved in water and extracted with ether. The latter was discarded. The aqueous layer was then acidified to

Congo red with HCl and extracted repeatedly with ether. This extract was concentrated in a molecular still for distillation of the residue. 135 mg. of distillate were collected up to an oil bath temperature of 200° and under a pressure less than 0.001 mm. The distillate was dissolved in ether and extracted with NaOH solution. The alkaline extract was then acidified with HCl. The acid material which separated was reextracted with ether. Since it could not be directly crystallized, it was redistilled in a microstill under 0.5 mm. pressure with the temperature of the oil bath raised to 250°. During this procedure, the production of an indole by decarboxylation was obvious from the odor of the distillate. 87 mg. of material were collected. This was dissolved in ether and shaken out with NaOH solution to remove undecomposed indole acids. The ether layer upon evaporation gave an oily indole fraction which was redistilled in a microstill. 7 mg. distilled up to 150° under 0.3 mm. pressure. The product melted at 80–100°. Upon recrystallization from 0.02 cc. of petroleum ether, 3 mg. of flat needles were obtained which melted at 108–112°.

When this was treated with an equivalent of picric acid in 0.15 cc. of ethyl alcohol, 3.2 mg. of red needles were obtained which melted at 182–186°. After recrystallization from alcohol the substance melted at 185–187°. A mixed melting point with the higher melting synthetic picrate obtained above showed no depression.

The final picrate was recombined with its mother liquor and evaporated to dryness. The residue (3.2 mg.) was treated with a small volume of sodium hydroxide and a few drops of ether. The ether layer was washed with NaOH solution until all color of picric acid had disappeared and then evaporated to dryness in a microstill for redistillation of the indole. 1.5 mg. distilled up to 150° and under 0.3 mm. This material melted at 115–116°. After recrystallization from 0.01 cc. of petroleum ether, 0.8 mg. of long flat needles was obtained which melted at 115–117°. A mixed melting point with the higher melting synthetic indole reported above showed no depression.

Since the supply of the pure, high melting indole from dihydrolysergic acid was exhausted in melting point determinations, there was not sufficient for analysis as the picrate or the indole itself.

Analytical data were obtained on a lower melting picrate (164–168°) obtained in a preliminary run as follows:

$C_{16}H_{14}O_7N_4$. Calculated, C 51.34, H 3.74; found, C 51.70, H 3.92

From the mother liquors of the purified indole, 2.2 mg. of indole were recovered which melted at 80–105°. A picrate (3 mg.) prepared from this melted at 175–183°. This was not recrystallized, since there was not enough for both recrystallization and analysis. The analysis gave C 51.90, H 4.06.

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