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Investigations on the Fischer indole synthesis I.

THE STRUCTURE OF A SUPPOSED INTERMEDIATE.

R.H.C. Elgersma and E. Havinga

Laboratory of Organic Chemistry, The University, Leiden, Postbox 75, The Netherlands.

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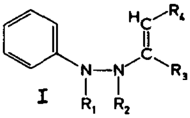
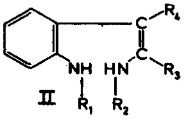
The proposal by Robinson and Robinson (1) for a mechanism of the Fischer indole synthesis (2) implies i.a. the occurrence of two intermediates: the phenylhydrazinoalkene I and the diamine II.



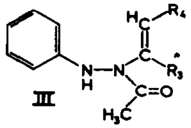
I

a: $R_1 = R_2 = COCH_3$
$R_3 = R_4 = CH_3$
b: $R_1 = R_2 = COCH_3$
$R_3, R_4 = -(CH_2)_4-$



II

a: $R_1 = H$ $R_2 = COCH_3$
$R_3 = R_4 = CH_3$
b: $R_1 = H$ $R_2 = COCH_3$
$R_3, R_4 = -(CH_2)_4-$



III

a: $R_3 = R_4 = CH_3$
b: $R_3, R_4 = -(CH_2)_4-$

To obtain supporting evidence for this mechanism Suvorov and coworkers (3) endeavoured to isolate and study compounds with these structures. By acetylating phenylhydrazones of several aliphatic ketones with acetic anhydride (p-toluenesulfonic acid as a catalyst) they succeeded in preparing a number of N,N'-diacetyl derivatives of I.

Treatment of Ia with aqueous sulfuric acid gave 2,3-dimethylindole; treatment with 5% KOH-ethanol at room temperature or with boiling 5% KOH water gave a product $C_{12}H_{16}N_2O$ (A). Substance A contains one acetylgroup and one active hydrogen (Zerewitinoff determination). Besides a positive isonitrile reaction was found (primary amino group). 2,3-Dimethylindole and acetamide are obtained from A by the action of dilute acids in the cold, or by heating A to 150°. From these data in combination with the IR spectrum it was concluded that the substance A is 3-acetylamino-2-(o-aminophenyl)-butene-2 (IIa), the monoacetyl derivative of the second intermediate.

In the course of a study (4) of the Fischer indole synthesis we intended to prepare the cyclohexene derivative IIb. Starting from Ib a substance $C_{14}H_{18}N_2O$ (B) was obtained under the conditions given by Suvorov. Treatment of Ib with boiling KOH-ethanol gave cyclohexanone phenylhydrazone; surprisingly, this phenylhydrazone could also be produced from B under the same conditions, as indicated by t.l.c. This seemed not well understandable assuming B to have structure IIb.

On acetylating B with acetic anhydride and p-toluenesulfonic acid we obtained Ib, in addition to 9-acetyl-1,2,3,4-tetrahydrocarbazole; reduction of B in methanol (Pd/C, normal pressure, room temperature) gave aniline. These results indicate that B has structure IIIb.

The NMR spectrum of B (Varian HA-100; solvent $CDCl_3$, TMS as an internal reference) is in complete agreement with this structure: two broad signals at $\delta = 1.63$ and $\delta = 2.18$, and a singlet at $\delta = 2.16$ (8 methylene H and 3 methyl H), a broad signal at $\delta = 5.78$ (1 vinyl H), a singlet at $\delta = 6.5$ (1 N-H, disappears on shaking of the solution with D_2O) and a multiplet between $\delta = 6.7$ and $\delta = 7.3$ (5 aromatic H). By double resonance experiments it was shown that the broad signal at $\delta = 5.78$ becomes a sharp singlet on irradiation with 217 cps.

For direct comparison we prepared A, melting point and IR spectrum identical with the data given by Suvorov. Aniline is formed on reduction of A, as indicated by t.l.c. The NMR spectrum confirms structure IIIa for compound A:
doublet at $\delta = 1.64$ (3H; J=7cps), singlet at $\delta = 1.84$ (3H), singlet at $\delta = 2.12$ (3H), quartet at $\delta = 5.57$ (1H; J=7cps), singlet at $\delta = 6.6$ (1H; disappears on shaking of the solution with D_2O), multiplet between $\delta = 6.6$ and $\delta = 7.3$ (5H).
Neither A nor B gave a positive isonitrile reaction.

It follows that treatment of the diacetyl phenylhydrazino-alkene with alkali leads to the loss of the acetyl group on N_α without rearrangement. The product, though possibly an intermediate on the route to a de-acetylated indole derivative, is not a derivative of the diamino compound of type II but rather the mono acetyl derivative of the phenylhydrazino-alkene I.

References

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N.N. Suvorov, N.P. Sorokina, Proc.Acad.Sci.USSR, Chem.Sect. 136, 151 (1961).
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