

THE SELECTIVE REDUCTION OF ISOFLAVON

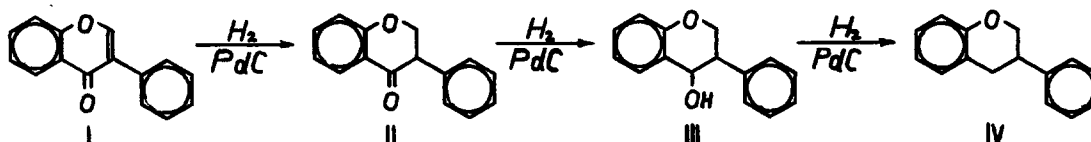
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In spite of biological and organic chemical significance of isoflavones with lower degree of oxidation, there is almost no general method for their synthesis. The usual way is by reduction of the isoflavones with noble metal catalysts¹⁻⁶. By this method each of the three compounds with lower degree of oxidation than that of isoflavones can be prepared. However the reduction reactions give a mixture so the required product is in low yield. There is no information to guide the selective catalytic reduction of the isoflavone to the required isoflavanone or isoflavan-4-ol.

We now describe a method by which the isoflavone /3-phenyl-chromon/ can be converted in nearly quantitative yield into either isoflavanone or isoflavan-4-ol using PdC-H₂ system. Use of PdC in ethanol, aqueous-ethanol, or aqueous-acetone yields α - and β -isoflavan-4-ol in almost quantitative yield /m.p.: 86-89°C; ref.m.p.: 4- α -ol: 97-97,5°C⁷, 4- β -ol: 75°C⁸/. The two isomers can be detected by t.l.c. on silica gel in benzene:ethanol 95:5 /Rf_{4- α -ol}: 0,48; Rf_{4- β -ol}: 0,54/. The α -isomer formed in greater quantity was isolated as its acetate /isoflavan-4- α -ol-acetate m.p.: 73-74°C, ref.m.p.: 72-73°C⁷/.



Thus the reduction of the isoflavone to isoflavan-4-ol on PdC is not stereospecific. The hydrogenation reaction is rapid, with no significant difference between the rate of the first and second mol hydrogen absorption. In the hydrogenation mixture ca. equal quantities of II and III can be detected after one mol hydrogen has been absorbed.

Isosflavan /IV/ forms when the isoflavan is hydrogenated in ethanol containing HCl or in acetic acid. The absorption of two moles of hydrogen is quick, that of the third is slow /m.p.:55°C, ref.m.p.:55°C⁸/.

We assumed that the hydrogenation depends on the polarity of the solvent, and therefore we extended our experiments to nonpolar and aprotic solvents. The isoflavan does not absorb hydrogen in benzene; however in dioxan one mol hydrogen is absorbed, but more slowly than in ethanol, and II forms almost quantitatively, in that case when Fluka PdC was used /isoflavanon m.p.:77°C; ref.m.p.:77°C³; 2,4-dinitrophenyl-hydrazone m.p.:207-208°C; ref.m.p.:209°C³/.

Using PdC catalyst obtained from other firms the reaction seems to be less selective.

The rate and direction of the hydrogenation reactions carried out in aqueous solutions is also influenced by the hydrogen ion concentration $[H^+]$. Therefore to obtain conditions for another selective reduction method, we used Britton-Robinson buffer in aqueous ethanol as solvent for the hydrogenation of the isoflavone. We established that the isoflavan absorbs two mol hydrogen between p_H 1 and 11,5. The rate of the absorption of both mols of hydrogen varies with the p_H . /The rate of hydrogenation was represented by the tangent drawn to the hydrogenation curve at the respective point. /The rates of the individual grades were: I \rightarrow II: $tg\alpha$; II \rightarrow III: $tg\beta$. /Fig.1./

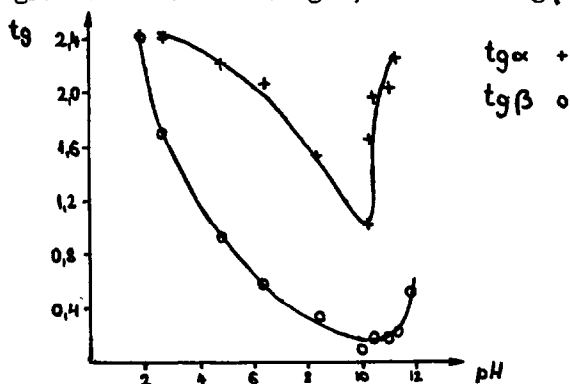


Fig. 4.

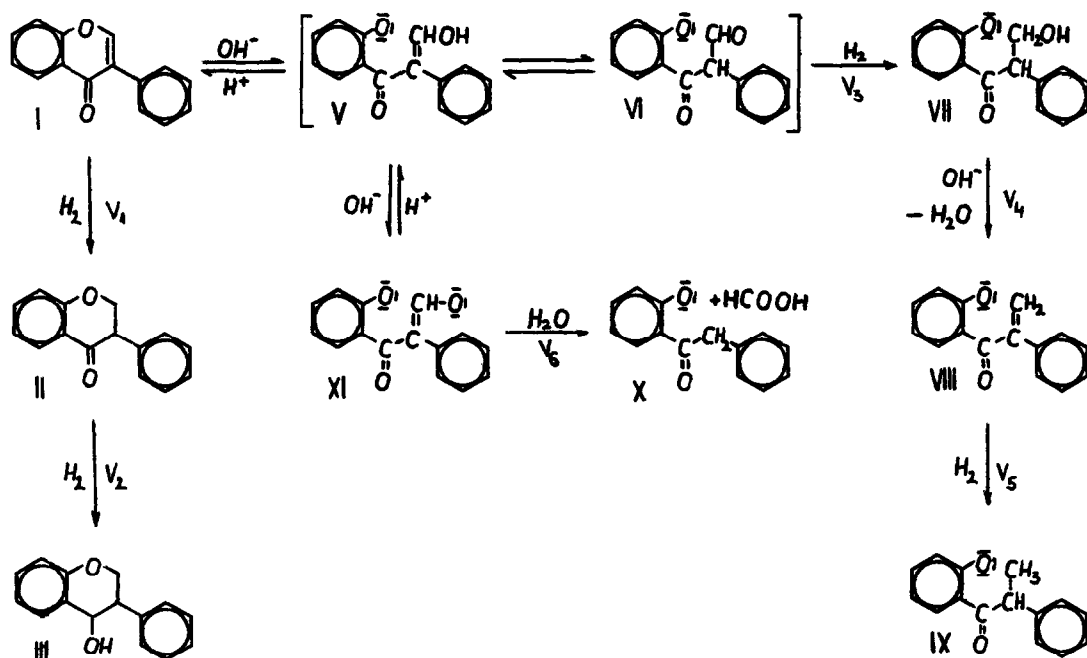
The significant difference between $tg\alpha$ and $tg\beta$ makes it possible to obtain the isoflavanone in 90 % by interrupting the reaction when one mol of hydrogen has been absorbed. Thus the hydrogenation of the isoflavone to isoflavanone can be made selective in an aqueous-alkaline buffer solution.

After the absorption of a second mol hydrogen / $p_H < 11$ / the main component in the reaction mixture is III. Above $p_H \geq 11,5$ the character of the hydrogenation is entirely changed. Two new components appear in the reaction mixture, the quantity of which increases with the increasing $[OH^-]$, until a certain value. One of the component could be identified as o-hydroxy-desoxybenzoin /X/. The

other new component, which was separated by column chromatography on Kieselgel PF₂₆₄, seemed to be another o-hydroxy-desoxybenzoin derivative from its t.l.c. behavior, FeCl₃-reaction and UV spectrum. On the bases of analytical, UV and IR spectroscopic investigations, this new component proved to be an o-hydroxy- α -methyl-desoxybenzoin /IX/, which was confirmed by synthesis /oil, o-hydroxy- α -methyl-desoxybenzoin-acetate m.p.:87-88°C; o-hydroxy- α -methyl-desoxybenzoin-benzoate m.p.:72-73°C/.

The buffer was not suitable for higher p_H-s than 12, so the hydrogenation was continued in aqueous-ethanol solution with different NaOH concentrations. In the course of the hydrogenation in 0,1-0,5 N NaOH solutions we could recover increasing quantities of unchanged isoflavon from the reaction mixture, which were in direct ratio to the NaOH concentration, and accordingly the quantity of the hydrogen absorption decreased.

In solution with p_H \geq 11, containing isoflavon, we would expect complicated equilibrium systems⁹. Depending on the p_H, the heterocyclic ring of the isoflavon opens, and the isoflavon and the opened forms are in equilibrium as shown below:



We could not detect VII or VIII in the reaction mixture. This fact proves, that the rate of the water elimination /according to the E_{1cB} mechanism⁹/ and that of the reduction of VIII, are more rapid than the $[V \rightleftharpoons VI]$ hydrogenation to VII. Thus, in this consecutive reaction series this last step of the process is rate determining $[V_3 < V_4 \leq V_5]$. The rate determining character of the proton elimination is confirmed by the $[OH^-]$ dependence of the hydrogenation. In alkaline media /over 11,5 p_H / the slowest process is the formation of II and III $[V_1 \ll V_3]$, because the equilibrium is shifted toward the direction of $[V \rightleftharpoons VI] \rightarrow XI$, depending on the measure of the $[OH^-]$ concentration; therefore the isoflavon concentration is small. The degradation of $[V \rightleftharpoons VI]$ to X $[V_6]$ is considerable, supported by the fact, that besides IX, X is the major by-product. The variation of the quantity of absorbed hydrogen in converse ratio to the increasing $[OH^-]$ /0,1-0,5/ N/is the preparative proof for the $V \rightarrow XI$ dissociation⁹. The Na-salt of XI is unsuitable for hydrogen absorption.

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