51. On Azohinokitiol (II).¹⁾

By Tetsuo NOZOE, Egai SEBE, and Seiji EBINE.

Chemical Institute, Faculty of Science, Tôhoku University; and the
Pharmacological Institute, Medical Faculty, Kumamoto University.

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Nozoe, Sebe et al.²⁾ found that, on coupling of the alkali salt of hinokitiol with diazonium salts of aniline, p-toluidine, β -naphthylamine and sulfanilic acid, orange to reddish-brown " α -azo" derivatives are formed, which, by warming with glacial acetic acid or ethanol containing a small amount of hydrochloric acid, converted to " β -azo" derivatives of dark reddish purple to dark purple color in good yield. The " α -form" is the true azo derivative (I) of hinokitiol, and the " β -form" was assumed by one of us (Nozoe)³⁾ to be a compound (II) having a quinone-like structure which was formed by the rearrangement accompanied by the cleavage of the azo group. He proposed to designate this unsaturated, 7-membered, quinone-like ring, the "tropoquinonoid" structure.

As to the position of the azo group, three points, i.e. 3, 5, and 7 (or o, p and o'), are possible of which, the most probable one was assumed to be 7 (or o')³⁾ where the steric effect is the smallest. However, no positive proof of this view had been obtained.

The present authors carried out experiments to clarify the structures of these compounds and the mechanism of this rearrangement, and also in order to offer these new type of compounds for the study on their physical and antibacterial properties, as well as their pharmacological actions.

As diazo components, the following amines were used: aniline, o- and p-toluidines, p-chloro-, p-bromo- and p-nitro-anilines, p-tolyl-azo-o-toluidine, p-sulfanilamide, and 2-methyl-5-nitraniline. In every case, as in previous cases²⁾, the primarily-formed " α -form" was easily converted to the " β -form". Whereas the compounds from aniline and p-nitraniline very easily underwent rearrangement,

that from p-anisidine was found to be rather stable. In any case, this conversion was found to be a characteristic reaction for azo-compounds of hinokitiol. The ultraviolet absorption spectra of these compounds will be reported elsewhere.

The " α -form" (m.p. 138°) of p-tolylazohinokitiol easily undergoes cleavage of N=N bond by reduction with zinc dust and acetic acid, alkaline hydrosulfite, or by catalytic hydrogenation.³⁾ Formation of p-toluidine and aminohinokitiol (m.p. 131°), as a result of this reduction, proves beyond doubt that this " α -form" is the true azo-derivative of hinokitiol. On the other hand " β -form" (m.p. 244°) absorbs 1 mole of hydrogen to give light colored "leuco-compound" which is re-oxidized by contact with air and returns to the original " β -form". Hence it is certain that this is no longer an azo compound but possesses a quinone-like structure formed by rearrangement. It is proposed, therefore, that the so-called " α -azohinokitiol" be called simply "azohinokitiol", and the " β -azohinokitiol" be designated "hinopurpurin", in future. p-Tolylazohinopurpurin gives red plates (m.p. $197-8^\circ$) on oxidation with permanganate and reddish orange prisms (m.p. 204° decomp.) on treatment with conc. nitric acid, the structures of which are both under investigation.

It is assumed that α -aminohinokitiol obtained by the reduction of p-tolylazohinokitiol is 5 (or p) -aminohinokitiol (VI) from its comparison with the three isomeric aminohinokitiols (α : m.p. 131° ; β : m.p. 99° ; γ : m.p. 121°)⁴⁾ obtained by the reduction of several kinds of mononitrohinokitiols. The bromination product of this p-tolylazohinokitiol, p-tolylazobromohinokitiol (m.p. 162°), and its " β -isomer", p-toluididobromohinopurpurin (m.p. 225°), were proved to be identical with the compound (IV; $\phi = p\text{-CH}_3\cdot\text{C}_6\text{H}_4\text{-}$)⁵⁾, obtained by the coupling of α -bromohinokitiol (V) with p-tolyldiazonium salt, and its " β -isomer", (VIII: $\phi = p\text{-CH}_3\cdot\text{C}_6\text{H}_4\text{-}$), respectively. This has

made it clear that the azo group in p-tolylazohinokitiol is situated, not at 7 (or o')-position as in (I), but at 5 (or p)-position as in (III). Other azohinokitiols are assumed to have the analogous constitution.

Although a definite proof is still lacking as to the structure of p-toluidido-hinopurpurin, there can be little doubt that this compound has the structure as shown in (VII: $\phi = p\text{-CH}_3\cdot\text{C}_6\text{H}_4\text{-}$), from the facts that this compound is formed by simply heating the " α -form" to its melting point, or very easily by warming the " α -form" in an acidic medium in which case a small amount of p-toluidine is invariably obtained as a by-product. The reaction mechanism of this rearrangement, which is catalysed by a proton, is assumed to be in the following scheme:

Considering the fact that the azo compounds⁽⁶⁾ of tropolone synthesized recently hardly show any tendency to undergo this sort of rearrangement, it is certain that the presence of the isopropyl group adjacent to the azo group has an important significance in this reaction. It can safely be presumed that this rearrangement ($X \rightarrow XI$) takes place by the steric pressure of the isopropyl group at an elevated temperature. Even from this point, the azo group must be at 5 (or p)-position, rather than at 7 (or o').

Experimental.

Preparation of Azohinokitiols (III) and Hinopurpurins (VII):—

(a) To a solution of sodium or potassium salt of hinokitiol, cooled to 0° to 5°, a solution of diazotized amines was added, and the coupling carried out by an ordinary method. The crude azohinokitiols were recrystallized from benzene, acetone or ethanol. Yield, 80–95%. Azohinokitiols derived from benzidine, p-aminobenzoic acid, and o-tolylazo-o-toluidine were all insoluble in common organic solvents, so that they were recrystallized as their K-salts and then freed by cold, dilute HCl. Azohinokitiols derived from aniline, and p-bromo- and p-nitro-anilines were so unstable that they easily underwent conversion to hinopurpurins during recrystallization. The latter was especially unstable, and practically impossible to purify.

(b) Azohinokitiols were boiled for 1–2 hrs. with ethanol containing a small amount of conc. HCl to effect conversion to hino-

purpurins. Azohinokitiols insoluble in ethanol (see above) were boiled for a long time in glacial acetic acid, with or without the addition of a small amount of conc. HCl. Yield, 60–80%.

(c) For the sake of simplification, azohinokitiol (III) and hinopurpurin (VII) are designated by α and β , respectively: [$\phi = \text{C}_6\text{H}_5$ –] α : red, m.p. 109°. Found: N, 10.19. $\text{C}_{16}\text{H}_{16}\text{O}_2\text{N}_2$ requires N, 10.44%. β : dark purple, m.p. 148°. Found: N, 10.11%. [$\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$ –] α : reddish brown, m.p. 138° β : dark purple, m.p. 244°. ²⁾ [$\phi = \text{o-CH}_3 \cdot \text{C}_6\text{H}_4$ –] α : reddish brown, m.p. 120–1°; β : reddish brown, m.p. >300°. [$\phi = \text{H}_2\text{N} \cdot \text{C}_6\text{H}_4$ –] α : reddish brown, m.p. >300°; β : dark purple, m.p. >300°. [$\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{N} = \text{N} \cdot \text{C}_6\text{H}_3(\text{CH}_3)$ –] α : reddish purple, m.p. 146–7°. Found: N, 12.41. $\text{C}_{22}\text{H}_{24}\text{O}_2\text{N}_4$ requires N, 14.00%; β : orange violet, m.p. 182–3°. Found: N, 14.24%. [$\phi = \text{HOOC} \cdot \text{C}_6\text{H}_4$ –] α : reddish orange, m.p. 196–7°. Found: N, 8.24. $\text{C}_{17}\text{H}_{16}\text{O}_4\text{N}_2$ requires N, 8.13%. β : dark purple, m.p. >300°. Found: N, 8.76%. [$\phi = \text{p-Cl} \cdot \text{C}_6\text{H}_4$ –] α : yellowish brown, m.p. 138–9°, β : dark purple, m.p. 256–7°. [$\phi = \text{p-Br} \cdot \text{C}_6\text{H}_4$ –] α : reddish brown, m.p. 150°. Found: N, 7.59. $\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}_2\text{Br}$ requires N, 8.07%. β : dark blue-violet, m.p. 236° (decomp.). Found: N, 7.88%. [$\phi = \text{p-NO}_2 \cdot \text{C}_6\text{H}_4$ –] α : reddish brown, β : dark purple, m.p. >300°. [$\phi = 2\text{-Methyl-5-nitrophenyl}$ –] α : yellowish brown, m.p. 218–9°, β : reddish brown, m.p. 233–4°. [$\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$ –] α : deep scarlet, m.p. 139.5°. Found: N, 8.95. $\text{C}_{17}\text{H}_{18}\text{O}_3\text{N}_2$ requires N, 9.39%. β : greenish black, m.p. 228–9°. Found: N, 9.35%. [$\phi = \text{p-HO}_2\text{S} \cdot \text{C}_6\text{H}_4$ –] α : reddish brown, m.p. >300°; β : reddish violet, m.p. >300°. [$\phi = \text{p-NH}_2\text{SO}_2 \cdot \text{C}_6\text{H}_4$ –] α : pale violet, m.p. 172–3°. Found: N, 11.91. $\text{C}_{16}\text{H}_{17}\text{ON}_3\text{S}$ requires N, 12.10%. β : dark purple, m.p. 245–7°. Found: N, 11.22%.

Formation of p-Toluidine during the Rearrangement of (III: $\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$ –) into (VII) This rearrangement was carried out by the procedures described in the foregoing, and after made alkaline, the reaction mixture was subjected to steam distillation. The distillate was extracted with benzen and from the extract, there was obtained 0.07 g. of p-toluidine, m.p. 45–6°, which was identified as p-acetotoluidide, m.p. and mixed m.p. 147°.

p-Toluidido-hinopurpurin (VII: $\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$ –):—(a) A pale brown product was obtained by the reduction of hinopurpurin with alkaline hydrosulfite, or zinc dust and glacial acetic acid. This product, however, regained its dark color immediately upon contact with air and, therefore, could not be purified. The filtrate, from which the reduction product was filtered, did not give p-toluidine. (b) In another experiment, hinopurpurin (0.2 g) in acetic acid solution was first catalytically hydrogenated until one mole of hydrogen was absorbed, and then reoxidized by shaking with air until one atom of oxygene was taken up, whereupon light

colored solution of "leuco-compound" regained its original reddish purple color, and the original hinopurpurin was recovered in quantitative yield. M.p. and mixed m.p. $244-5^{\circ}$. (c) On oxidation with permanganate in acetone solution, a small amount of red plates, m.p. $197-8^{\circ}$, was obtained. (d) 1.5 g. of finely powered (VII) was added in small portions to 10 cc. of conc. HNO_3 at a temperature below 30° , then heated on a water bath for 5 minutes, and finally cooled. The reddish powder that separated out (1.69 g.) was recrystallized from acetone in reddish orange prisms, m.p. 204° (decomp.). (Found: C, 48.55; H, 3.25; N, 14.29%).

5-p-Tolylazo-7-bromohinokitiol (IV: $\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$):—1 g. of (III: $\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$) was dissolved in 20 cc. of chloroform and, while stirring in an ice-bath, 0.6 g. of bromine dissolved in 2 cc. of chloroform was added dropwise. The solvent was then removed at a room temperature, and the solid residue was recrystallized from acetone in reddish orange needles, m.p. 162° . (Yield, 0.22 g.), and greyish violet crystals, m.p. 202° . The former showed no depression of m.p. on admixture with (IV: $\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$) obtained by the azo-coupling of (V).

p-Toluidido-monobromohinopurpurin (VIII: $\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$):—0.2 g. of (IV: $\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$) obtained from (III) was rearranged as in the foregoing, and the crude product was recrystallized from glacial acetic acid in dark greenish violet crystals, m.p. 225° . (Yield, 0.12 g.) This substance did not show any depression of m.p. when mixed with (VIII: $\phi = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4$) obtained from (V) through (IV).

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