63. On Sulfonic Acid Derivatives of Hinokitiol.

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Hinokitiol (I) possesses a semi-aromatic character and easily undergoes halogenation, nitration and azo-coupling. Notwithstanding this show of aromaticity, it had been impossible to carry out sulfonation due to the stability of hinokitiol against heating with concentrated or fuming sulfuric acid for a long hours at 100–150°. The authors assumed that this was due to the amphoteric character of hinokitiol which acted like a base in strong acids, such as sulfuric acid, and took the conjugate acid (II) form by accepting a proton. As a result, the tropolone nucleus would be positively charged, building up resistance against cationoid reagents. The correctness of this assumption is confirmed by the fact that the nitration of hinokitiol by concentrated nitric acid proceeds vigorously in glacial acetic acid, whereas the reaction is strongly obstructed under the presence of concentrated sulfuric acid.

It would be vastly advantageous to obtain water-soluble compounds of hinokitiol and its derivatives by sulfonation for the pharmacological study of compounds of such an unique structure. For this reason, the present authors undertook this experiment by various methods.

As a sulfonation agent, chlorosulfonic acid was employed, and was applied to the sodium or silver salt of hinokitiol, but resulted in the total recovery of the free compound (I).

Under the assumption that a thermal reaction of hinokitiol (I) and sulfamic acid (III) in non-aqueous solvent or without the solvent, would result in sulfonation with liberation of ammonia, rather than formation of a conjugate acid (II), an equimolar mixture of (I) and (III) was heated to 150–170°. For the first time, a watersoluble product was obtained as pale yellow plates, m.p. 235–237°.
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(dec.), the analytical values of which pointed to an ammonium salt of a monosulfonic acid. This compound gave mono- and di-potassium salts by potassium hydroxide, disodium salt by sodium hydroxide, and a water-insoluble barium salt by barium hydroxide. A free sulfonic acid (IV), obtained from the barium salt by sulfuric acid, however, was found to be deliquescent crystals, very easily soluble in water. This acid (IV) can easily be identified by its aniline salt of m.p. 214-215°, or p-toluidine salt of m.p. 214-215°. Since this acid (IV) and its alkali salts easily give complex salt with iron and copper, it is certain that it is hinokitiol-monosulfonic acid, still retaining the tropolone structure.

By the addition of bromine to the aqueous solutions of alkali salts of (IV), two kinds of monobromo-compounds (Va, Vb) are formed by the absorption of 1 molecule of bromine, and then to dibromo-compound (VI) by a further absorption of another molecule.

Coupling of (IV) with p-tolylidiazonium salt gives an orange azo-compound (VII) which seems to undergo hinopurpurin-type rearrangement as it changes to reddish purple when its monopotassium salt (orange) is heated with acetic acid. However, its dipotassium salt (orange red) changes by similar treatment to a paler compound. Monobromosulfonic acid (Va) also undergoes azo-coupling. Further studies are needed for these compounds.

As to the position of the sulfonic acid group, that at 7-, i.e. o'-position (IV) where it is most suitable by steric configuration, is the most likely, considering the steric effect (thermal reaction) and the ortho or the hydrogen-bond effect. This can, in part, be understood from the difficulty in sulfonation of α-monobromohinokitiol, and α- and β-dibromohinokitiol (o, o' and o', p), in which the 7-, or o'-position is thought to be occupied, whereas β-(o) (VIII) and γ-monobromohinokitiol (p) (IX), in which 7-, or o', is thought to be vacant, are so easily sulfonated.

It is another confirmation of this point that (Va) and (Vb), obtained by the monobromination of (IV), were also obtained by the sulfonation of (VIII) and (IX), respectively. It is the belief of the authors that it would be possible to utilize this method of sulfonation as a means of determining the position of substituents in a hinokitiol molecule. The dibromosulfonic acid compound (VI) is almost colorless, and gives only a very slight coloration by ferric chloride, which may be interpreted as resonance inhibition by the three substituents.

Experimental.

Sulfonation of Hinokitiol (I) by Sulfamic Acid (III): — A mixture of 1.5 g. of (I) and 1 g. of (III) is heated to 150-170° for 6 hours.

Hinokitiol-Monosulfonic Acid (IV): — Obtained by the addition of the calculated amount of H_{2}SO_{4} to the Ba-salt. Deliquescent crystals. Aniline Salt: —— By warming (IV) with aniline, or by warming monoalkali salt of (IV) with aniline and HCl. Pale yellow plates (from alcohol) or needles (from water), m.p. 214-215°. Anal. Caled. for C_{10}H_{16}O_{9}NS : C, 56.95; H, 5.67; N, 4.15. Found: C, 56.89; H, 5.78; N, 4.02. p-Toluidine Salt: —— By a similar manner. Pale yellow prisms (from water), m.p. 214-215°. Anal. Caled. for C_{12}H_{14}O_{9}NS : C, 58.10; H, 5.6; N, 3.99. Found: C, 58.1; H, 5.63; N, 4.02. Cu-Complex Salt: — (a). By adding an excess of CuSO_{4} to the Ba-salt, filtering and evaporating the filtrate. This residue is dissolved in alcohol, filtered, and the filtrate evaporated. Yellowish green needles from acetone. Anal. Caled. for C_{10}H_{16}O_{9}SCu : Cu, 20.78 Found: 20.81. (b). By adding 1/2 mole of CuSO_{4} to the ammonium salt and evaporating. Green needles. Anal. Caled. for (C_{10}H_{16}O_{9}SN)_{2} Cu : Cu, 10.88. Found: 10.89. Fe-Complex Salt: —— By adding
1/6 mole of \( \text{Fe}_2(\text{SO}_4)_3 \) to the ammonium salt and evaporating. Dark red crystalline powder. Anal. Caled. for \( (\text{C}_9\text{H}_{10}\text{O}_4\text{SN})_3 \text{Fe} \): Fe, 6.72 Found: 6.70.

**Monobromohinokitiol Sulfonic Acid (Va, Vb):**—1.4 g. of mono-K-salt of (IV) is dissolved in water and 0.8 g. of \( \text{Br}_2 \) added in cold state, whereby \( \text{Br}_2 \) is quickly absorbed. Addition of KOH to pH 1.2 yields pale yellow precipitate (1.3 g.). Mainly mono-K-salt of (Va). Aniline salt (A), pale yellow scales from water, m.p. 204–205°. Further addition of KOH to pH 3.0 gives more pale yellow precipitate (0.2 g.). Mono-K-salt of (Vb). Aniline salt (B), yellow plates from water, m.p. 211–212°. On admixture of (A) and (B), m.p. was depressed. Anal. Caled. for \( \text{C}_{10}\text{H}_{10}\text{O}_4\text{SNBr} \): C, 46.12; H, 4.36. Found: (A), C, 45.86; H, 4.21, (B), C, 46.30; H, 4.13.

**Sulfonation of \( \beta \)-Monobromohinokitiol (VIII):**—Sulfonated as in the case of (I). Aniline salt, m.p. 204–205°. Mixed fusion with (A) gave no depression of m.p. Sulfonation of \( \gamma \)-Monobromohinokitiol (IX):—Sulfonated as above. Aniline salt, m.p. 211–212°. Mixed fusion with (B) gave no depression of m.p.

**Dibromohinokitiol Sulfonic Acid (VI):**—Addition of a further mole of \( \text{Br}_2 \) to the aqueous solution of mono-K-salt of (V). \( \text{Br}_2 \) is gradually absorbed and the addition of 1 mole of KOH with subsequent evaporation yields mono-K-salt of (VI). Colorless plates. Very weak coloration by \( \text{FeCl}_3 \). Anal. Caled. for \( \text{C}_{10}\text{H}_{10}\text{O}_4\text{SBr}_2\text{K} \): K, 8.88. Found: 8.41.

**Azo-Coupling of (II) and (Va):**—Di-K-salt of (II) is coupled with p-tolyl diazonium salt in the usual manner, and a mono-K-salt is obtained as an orange precipitate. Addition of 1 mole of KOH gave di-K-salt, soluble in water. Crystallized to orange red scales, from alcohol. This color changes according to pH, like methyl orange. Azo-coupling of (Va) was also carried out in the same manner.

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**References.**

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