33. Chlorobromo and Polybromo Substitution Products of Hinokitiol.

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The authors have been able to predict with reasonable accuracy the substituent positions in various halogenohinokitiols by the use of ordinary methods of organic chemistry¹⁰⁾ as well as the values of dipole moment measurements¹⁾. Recently, structural determination of the products of benzylic acid rearrangement of the various nitrohinokitiols²⁾, and the Sandmeyer reaction of various aminohinokitiols^{3, 4)}, carried out at the same time as the present experiments, have confirmed the correctness of assumptions drawn heretofore regarding the substituent positions in monochloro- and monobromo-hinokitiols.

The present experiments were undertaken in order to determine the structures of chlorobromo- and tribromo-hinokitiols, and to further observe the bromination of hinokitiol.

The manner of numbering and position designations of tropolone nucleus are shown in (A)¹⁰⁾.

α -Chlorobromohinokitiol (I), m.p.

142°.

Obtained from β -, i.e. o-chlorohinokitiol by its bromination in ethanol, under the presence of sodium acetate, at 0° to 3°, as colorless crystals, m.p. 140°. This compound was found to be identical with α -chlorobromohinokitiol⁶⁾, m.p. 140–141°, obtained by the chlorination⁵⁾ of α -, i.e. o'-bromohinokitiol, so that it is certain that (I) is o-chloro-o'-bromohinokitiol (B: X₁ = Cl, X₂ = H, X₃ = Br). β -Chlorobromohinokitiol (II), m.p. 88°.

This compound⁶⁾ had previously been obtained either by the chlorination⁵⁾ of α -, i.e. o'-bromohinokitiol, or by the bromination⁵⁾ of α -, i.e. p-chlorohinokitiol. From the course of its formation, it had seemed beyond doubt that (II) was p-chloro-o'-bromohinokitiol but its confirmation was made by the present experiments. Catalytic reduction of the p-tolylazo compound⁷⁾, m.p. 170°, of o'-bromohinokitiol yielded p-amino-o'-bromohinokitiol as yellowish brown crystals, m.p. 157° (Anal. Calcd. for C₁₀H₁₂O₂NBr: N, 5.43. Found: N, 5.33)⁸⁾, giving a diacetyl compound, m.p. 185° (Anal. Calcd. for

$C_{14}H_{16}O_4NBr$: N, 4.09. Found: N, 4.57). The Sandmeyer reaction of the amino compound yielded pale yellow needles (II), m.p. 87–88°, which gave no depression of the melting point when fused with compounds obtained as described above⁵⁾. It follows, therefore, that (II) is p-chloro-o'-bromohinokitiol (B: $X_1 = H$, $X_2 = Cl$, $X_3 = Br$).

δ -Chlorobromohinokitiol (III), m.p. 117.5°: p-Toluidine compound, m.p. 107.5°.

Bromination of γ -, i.e. o'-chlorohinokitiol under the presence of sodium acetate and under ice-cooling, yields pale yellow plates (III), m.p. 113.5°, in ca. 70% yield, giving a p-toluidine compound of m.p. 108.5°. This compound is identical with δ -chlorobromohinokitiol⁶⁾, m.p. 116.5–117.5° (p-toluidine compound, m.p. 107.5°) obtained by the chlorination of β -, i.e. o-bromohinokitiol. Their mixed melting points were 113–114° and 107.5°, respectively. Therefore, (III) is undoubtedly o'-chloro-o-bromohinokitiol (B: $X_1 = Br$, $X_2 = H$, $X_3 = Cl$).

ϵ -Chlorobromohinokitiol (IV), oil: p-Toluidine compound, m.p. 128–129°.

This compound had previously been obtained as a by-product during the chlorination of β -, i.e. o-bromohinokitiol. Bromination of α -, i.e. p-chlorohinokitiol in ethanol failed to yield this, besides (II) and a smaller amount of colorless plates, m.p. 129°. Nothing definite can, therefore, be said as to this structure until more detailed study has been made.

ζ -Chlorobromohinokitiol (V), m.p. 84°.

Heating γ -, i.e. o'-chlorohinokitiol in glacial acetic acid with 1 mole of bromine yields (III) and a smaller amount of pale yellow needles (V), m.p. 84°, a new, hitherto unknown compound. Anal. Calcd. for $C_{10}H_{10}O_2BrCl$: C, 43.27; H, 3.63. Found: C, 43.52; H, 3.63. p-Toluidine compound, m.p. 92°. On the other hand, yellow crystals melting at 112–113° are obtained by the chlorination of p-bromohinokitiol in alcohol, under ice-cooling, so that more detailed studies must be made as to this points.

β -Dibromohinokitiol (VI), m.p. 94°.

Bromination of either α -, i.e. o'-bromohinokitiol or hinokitiol itself in glacial acetic acid yields (VI)⁷⁾. From the result of dipole moment measurements¹⁾, it had been assumed as o',p-dibromocompound. During the course of the present experiments, (VI), m.p. 90.5–92°, was obtained by the Sandmeyer reaction of p-amino-o'-bromohinokitiol, the mixed m.p. with the compound obtained by the foregoing method showing m.p. 91.5–92.5°, confirming the structure of (VI) as o',p-dibromohinokitiol (B: $X_1 = H$, $X_2 = X_3 = Br$).

β -Tribromohinokitiol (VII), m.p. 90–91.5°.

Previously, Sebe had obtained tribromohinokitiol, m.p. 88°, from (VI), and later observed that this m.p. could be raised to 96°⁹⁾. In the present experiments, (VII) was obtained from (VI) as well as from o, o'-dibromohinokitiol. The bromination of (VI) in glacial acetic acid under the presence of sodium acetate, yielded (VII) in a 50% yield, with a by-product of colorless needles, m.p. 176°, which gave no coloration with ferric chloride.

(VII) was also obtained in a 15% yield from o, o'-dibromohinokitiol by allowing the suspension of its sodium salt in carbon tetrachloride to stand overnight with bromine. The mixed fusion of (VII) and the tribromo compound obtained by Sebe gave a m.p. 78–85°. Since they are apparently different compounds, the one obtained by Sebe was designated α -tribromohinokitiol, and the one obtained by the present authors, β -tribromo compound. (VII) is yellowish orange crystals, m.p. 90–91.5°, as recrystallized from a mixture of petroleum ether and benzene in which solvent (VII) is more easily soluble than the two dibromo compounds. Anal. Calcd. for $C_{10}H_9O_3Br_3$: C, 29.96; H, 2.26. Found: C, 29.80; H, 2.56. (VII) is unstable to alkalis and generally give sodium salt and molecular compounds of deep color. **Aniline compound:** Orange microcrystals, m.p. 92–94°. Anal. Calcd. for $C_{16}H_{16}O_2NBr_3$: N, 2.84. Found: N, 2.93. **p-Toluidine compound:** Orange microcrystals, m.p. 125–126°; practically insoluble in petroleum ether and benzene, a mixture of which can be used in separating the unreacted material. Anal. Calcd. for $C_{17}H_{18}O_2NBr_3$: N, 2.76. Found: N, 2.67. **Diethylamine compound:** Reddish orange crystals. Anal. Calcd. for $C_{14}H_{20}O_2NBr_3$: N, 2.96. Found: N, 2.72.

Reëxamination of the Bromination of Hinokitiol:

Up to the present, p-bromohinokitiol had been obtained only by the Sandmeyer reaction of p-aminohinokitiol⁹⁾. Attempt was made to obtain it by the direct brominations of hinokitiol. In order to avoid the hydrogen-bond effect (ortho effect)¹⁰⁾ during substitution, bromination of its isopropyl ether was carried out, and separately in a boiling glacial acetic acid in consideration of the temperature effect¹⁰⁾. In either case, p-bromohinokitiol did not seem to have been formed¹¹⁾, the products being mostly oil or resinous substances. Bromination of hinokitiol isopropyl ether in ethanol or carbon tetrachloride at -15° to -20° yields o-bromo and o, o'-dibromohinokitiols. The same reaction in water, under ice-cooling yields, even with 1 mole of bromine, p, o'- and o, o'-dibromohinokitiols. Consequently, it was found that ethers are similarly, or perhaps more easily, brominated as hinokitiol itself. Application of 1 mole of bromine (to hinokitiol) in boiling glacial acetic acid yields only o'-

bromohinokitiol, with recovery of hinokitiol in a fair amount. In the case of 2 moles of bromine, the products are (VI) and a new γ -dibromohinokitiol (VIII), pale orange needles, m.p. 103–104°. Anal. Calcd. for $C_{10}H_{10}O_2Br_2$: C, 37.30; H, 3.13; mol.wt., 322. Found: C, 37.92; H, 3.62; mol.wt., 310. (VIII) absorbs further moles of bromine in acetic acid solution under the presence of sodium acetate to yield crystals which gives a p-toluidine compound, m.p. 145–146°. Anal. Calcd. for $C_{17}H_{18}O_2NBr_3$: N, 2.76. Found: N, 2.89. No detailed study could be made due to the lack of material.

If the three positions in the hinokitiol nucleus that are susceptible to electrophilic substitution are o, o' and p, then the total number of chlorobromo compounds that can theoretically be formed is six, of which three have been structurally determined by the present series of experiments. The other two are the o, p-substituted compounds which are hardly possible of formation due to the steric effect¹⁰. Final decision on the structure of the two tribromohinokitiols must await further detailed study.

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- 11) During treatment of oily bromination products of hinokitiol, some needle crystals of m.p. 102° were obtained. This was confirmed by mixed fusion to be p-bromohinokitiol obtained by the Sandmeyer reaction of p-aminohinokitiol.