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From its structural standpoint\(^1\), hinokitiol (4-isopropylcycloheptatriene-2, 4, 6-ol-2-one-1) is liable to undergo electrophilic substitution at 3, 5 and 7 (i.e., o, p and o' proposed by the authors). It follows, therefore, that hinokitiol would give 3 kinds of mono- and di-substituted, and one of tri-substituted bromination products.

Nozoe, Sebe and their coworkers\(^3\) carried out the bromination of hinokitiol under various conditions, and obtained one kind of monobromo compound (m. p. 56°), two kinds of dibromo compounds (α: m. p. 134°; β: m. p. 96°), and one kind of tribromo compound (m. p. 88°). From the course of formation of these compounds\(^3\), and the measurement of dipole moments\(^2\), it was assumed that monobromo compound (m. p. 56°) was substituted at 7 or o' (I), α- and β-dibromo compounds at 3, 7 (o, o') (II), and at 5, 7 (o', p) (III), respectively. Not only in this case, but also in the case of chloro and nitrocompounds, only two out of the three possible compounds of di-substituted products can be obtained. In short, the steric hindrance is so great in (IV) that, even if a di-substitution does occur, it is further brominated by the excess of the reagent, resulting in a tri-substituted compound (V).

\[\begin{align*}
\text{(I)} & \quad \text{Br} \quad \text{O} \quad \text{H} \\
\text{(II)} & \quad \text{Br} \quad \text{O} \quad \text{H} \\
\text{(III)} & \quad \text{Br} \quad \text{O} \quad \text{H} \\
\text{(IV)} & \quad \text{Br} \quad \text{O} \quad \text{H} \\
\text{(V)} & \quad \text{Br} \quad \text{O} \quad \text{H} \\
\text{(VI)} & \quad \text{Br} \quad \text{O} \quad \text{H}
\end{align*}\]

3) Nozoe, Sebe et al.: To be published.
More than two kinds of isomers are always obtained for a mono-substituted chloro and nitro compounds\(^1\), whereas only one monobromo compound has been obtained to date. Formula (I) has been given as the most probable one for this monobromo compound but nothing definite has been obtained. It seemed better to withhold judgement until comparison could be made of the chemical and physical properties of the three possible isomers. For this reason, examinations of bromo derivatives, as well as of the chloro- and iodo-derivatives\(^\) were again carried out.

Research for new isomers unexpectedly came up against many difficulties but a second isomer, melting at 41.5°C, was newly isolated. The first one of m.p. 56°C was named \(\alpha\)-, and the new one of m.p. 41.5°C was designated \(\beta\)-monobromohinokitiol. The bromination had been carried out at 0° to 20°, but the present one was carried out in alcohol (absolute or hydrated) at a low temperature of -10° to -15°, using 0.5 to 1 equivalent of bromine. Treatment of the bromination products gave, besides the hitherto (I) and (II), the new \(\beta\)-monobromohinokitiol in 20–25% yield. Further bromination of (I) gives (II) and (III)\(^9\), but the same treatment of the new \(\beta\)-compound gave only (II) in a good yield, which seemed to indicate that formula (VI) would be the most likely one for the \(\beta\)-monobromo compound.

Recently, a \(\gamma\)-isomer (m.p. 102°C)\(^9\), which is assumed to be 5- or \(\rho\)-monobromohinokitiol, was obtained from toluolazohinokitiol through its \(\alpha\)-amino compound, which brings the total number of isomers to the three that are possible. The dipole moments of these compounds are being determined.

The relationship between the kind of products obtained and the yield according to the conditions of reaction is generally very complicated. However, one point to be noted here is the fact that there seems to be no difference in the rate of substitution by the lowering of the reaction temperature, the decrease in the yield of (I) being accompanied by the increase not only of (VI) but also of (II) This must be due to the fact that the steric hindrance of isopropyl group at 4 decreases with the lowering of the reaction temperature and, at the same time, the tendency for substitution at 3 (or 5) increases by the inductive effect (+I) of the isopropyl group\(^9\). Upon the formation of (VI), its most active position, that at 7, is vacant so that this point is immediately substituted, increasing the yield of (II). On the other hand, at a higher temperature, either side of the isopropyl group becomes increasingly

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4) Nozoe et al: Cf. the following article in this number of the Proceedings.
difficult to substitute, so that the bromination of (I) becomes more difficult.

Chlorination of (VI), however, gave a new δ-monochloro-mono-bromohinokitiol (VII) of m.p. 117.5°, and a small amount of liquid substitution product, instead of the heretofore obtained monochloro-omonobromo compounds\(^5\) (α: m.p. 142°; β: m.p. 88°; γ: m.p. 68°). The compounds (VI) and (VII), as are other halogen compounds obtained to date, give crystalline molecular compounds with aniline, toluidine and diethylamine.

Nitration of (VI) gave a very poor results although in this case, also, two new bromonitro compounds\(^6\) of m.p. 100.5–101.5° (γ) and or m.p. 149–150° (δ), respectively, were obtained, being different from those obtained to date (α: m.p. 134°; β: m.p. 112°). These new compounds are now being studied.

**Experimental**

\(\beta\)-Monobromohinokitiol (VI):

\(\alpha\) 2.0 g. of hinokitiol is dissolved in 15 cc. of 80% ethanol, 1.95 g. of bromine dissolved in 2 cc. of chloroform is added dropwise over a period of 15 minutes, while stirring the solution under ice-cooling (2–5°). After allowing the reaction mixture to stand for some time, it is poured into water, and the oily layer is taken up in benzene. The products are separated by the difference in acidity, (II), m.p. 133° (0.1 g.), and (I), m.p. 56° (0.4 g.), being obtained from the fraction forming sodium salts by shaking the benzene layer with saturated NaHCO\(_3\) solution. The Na-salt formed by 2N–Na\(_2\)CO\(_3\) solution is repeatedly recrystallized from warm water to obtain the insoluble portion which gives a free compound of m.p. 30–35° (0.2 g.). This is sublimated under reduced pressure and recrystallized from petroleum ether to colorless needles, m.p. 41.0–41.5°. Mixing this and (I) results in liquefaction at room temperature. (Found: C, 49.31; H, 4.23. Neutr. equiv. 235. \(C_{10}H_{11}O_3Br\) requires C, 49.38; H, 4.52%. Neutr. equiv. 243). From the readily soluble portion, (II) and (I) are obtained besides recovery of unchanged hinokitiol. (b) To a solution of 4.1 g. of hinokitiol dissolved in 30 cc. of 95% ethanol, a solution of 3.6 g. of bromine in 4 cc. of CCl\(_4\) is added dropwise over a 40-minute period, while stirring the solution under cooling (–15°). After allowing the mixture to stand for some time, the mixture is treated as in (a), and 0.48 g. of (VI), m.p. 36°, is obtained besides (I), (II), unchanged substance and an oily matter. (c) To a solutions of 32.8 g.

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5) Cf. 1) for the heretofore known chlorobromo-and bromonitro-compounds. Details will be published shortly.
(0.2 mol) hinokitiol dissolved in 480 cc. of 80% ethanol, a solution of 16 g. (0.1 mol) of bromine in 16 cc. of CCl₄ is added dropwise over a 50-minute period, while stirring the solution under ice-cooling (−15°). After allowing the mixture to stand for 1.5 hours, the mixture is poured into water, and treated as in (a). Yield of (VI) of m.p. 30° total 5.04 g. which is about 21/2 of theory.

**Molecular compounds of β-Monobromohinokitiol (VI):**

(a) **Aniline compound**—No crystalline product is obtained by the addition of aniline to (VI). Addition of petroleum ether and subsequent cooling precipitates yellow prismatic crystals, m.p. 63–64°. (Found; C, 57.15; H, 5.52. C₁₆H₁₈O₂NBr requires C, 57.15; H, 5.40%). A mixed m.p. with the aniline compound of (I) (m.p. 83°) is 60–73°.

(b) **p-Toluidine compound**—Crystallizes immediately by melting (VI) with p-toluidine, m.p. 74–74.5°. Recrystallizes from petroleum ether to yellow prisms (Found; N, 4.28. C₁₇H₂₁O₂NBr requires N, 4.00%).

(c) **Diethylamine compound**—Addition of diethylamine results in crystallization with generation of heat. Recrystallized from benzene to pale yellow, scaly crystals of m.p. 160–161°. (Found: N, 3.90. C₁₄H₂₂O₂NBr requires N, 4.43%).

**Further bromination of (VI):**

(a) 0.12 g. of (VI) is dissolved in 0.9 cc. of ethanol, and a solution of 0.08 g. of bromine in 0.4 cc. of CCl₄ is added under the presence of 0.11 g. of sodium acetate. 0.14 g. of (II), m.p. 132–133°, is obtained which is proved by mixed m.p. with an authentic product. (b) To the solution of 1.0 g. of (VI) dissolved in 5 cc. of glacial acetic acid is added a solution of 0.7 g. of bromine in 3.5 cc. of glacial acetic acid, while stirring the mixture under ice-cooling. White crystals precipitate out during this reaction. After allowing the mixture to stand for 1.5 hours, the crystals are collected on a filter. 1.2 g. of crystals melting at 128–129° are obtained, which give an m.p. of 132–133° after purification. No depression in m.p. was shown by admixture with (II).

**Chlorination of (VI):**

1.46 g. of (VI) is dissolved in 2 cc. of glacial acetic acid, and while stirring the solution at 15–20°, 160 cc. (at 30°, 760 mm) or 0.45 g. of chlorine gas is passed through the solution during a 55-minute period. Stirring is continued for a further 30 minutes while white crystals begin to precipitate out. Crystals melting at 105–110° are obtained in an yield of 0.45 g. Recrystallized from petroleum ether to slightly greenish plates of m.p. 116.5–117.5°. Since this compound does not coincide with any of α-, β- or γ-chlorobromo-hinokitiol, it was designated as the δ-isomer (VII). (Found: C, 43.56; H, 3.74. C₁₀H₁₀O₂BrCl requires C, 43.26; H, 3.63%). **Aniline compound**—Pale yellow, microcrystalline substance, m.p. 90.5–91.0°. (Found: C, 51.78; H, 4.29. C₁₀H₁₀O₂NBrCl requires C, 51.83; H, 4.62%). **p-Toluidine compound**
On β-Monobromohinokitiol.

—Pale yellow, micro-crystalline substance, m.p. 106–107°. (Found: C, 53.39; H, 4.68. C_{17}H_{19}O_{2}NBrCl requires C, 53.08; H, 4.98%).

Diethylamine compound—Yellow scaly crystals, m.p. 158–160°. (Found: C, 48.15; H, 6.32. C_{14}H_{21}O_{2}NBrCl requires C, 47.94; H, 6.04%). From the mother liquor of δ-chlorobromo compound (VII), unchanged (VI) was recovered besides an oily substance which gives a p-toluidine compound of m.p. 127–128°. (Found: N, 3.49. C_{17}H_{19}NOBrCl requires N, 3.64%).

Nitration of (VI):—1 g. of (VI) is dissolved in 1 cc. of glacial acetic acid, and while stirring the solution under ice-cooling, 0.5 g. of conc. nitric acid (sp. gr. 1.4) is added dropwise over a 20-minute period. Stirring is then continued for further 1.5 hrs., the mixture poured into water, and the reddish-brown oil that precipitates out is extracted with benzene. By shaking this benzene layer with 2-N sodium acetate solution, Na-salt of red, scaly crystals is obtained from which 0.04 g. of pale yellowish orange crystals of m.p. 85–95° are obtained. Recrystallization from a mixture of petroleum ether and benzene yields crystals of m.p. 100.5–101.5°. This was designated as the γ-isomer (VIII). (Found; C, 41.50; H, 3.25. C_{10}H_{10}O_{4}NBr requires C, 41.68; H, 3.50%).

p-Toluidine compound—Yellow, micro-crystalline substance, m.p. 143°. (Found: N, 7.04. C_{17}H_{19}O_{4}N_{2}Br requires N, 7.09%). From the Na-salt formed by a saturated NaHCO_{3} solution, another pale green crystals, m.p. 149–150°, were obtained. Its p-toluidine compound is yellowish orange micro-crystallin substance, m.p. 128–130°.

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