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The Structures of the Products from the Reaction of 3-Bromotropolone and 7-Bromohinokitiol with Caustic Alkali

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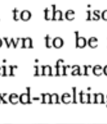
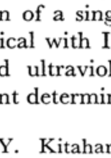
The main products from the reaction of 3-bromotropolone and 7-bromohinokitiol with caustic alkali are proved not to be 3-hydroxytropolone and 7-hydroxyhinokitiol, but 4-hydroxytropolone and 6-hydroxyhinokitiol. The mechanism of this abnormal substitution reaction is then discussed.

The formation of a hydroxytropolone, mp 227°C, by the treatment of 3-bromotropolone (I) with 75% potassium hydroxide has been reported by Nozoe and his coworkers,[1] whereas Cook and his coworkers have reported a hydroxytropolone, mp 244°C, obtained from I by the action of 50% sodium hydroxide.[2] Each group regarded its substance as being 3-hydroxytropolone. However, some years later, Nozoe and Kitahara found that 3-hydroxytropolone (II), mp 139°C, was obtained when I was treated with sodium methoxide,[3,4] while the previously-obtained compound, mp 227°C, was actually 4-hydroxytropolone (III).[3,5]

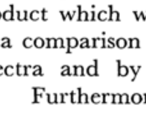
On the other hand, Lin and his coworkers have reported the formation of 7-hydroxyhinokitiol (IV),[6] mp 59°C, when 7-bromohinokitiol (V) was treated with 50% sodium hydroxide under the conditions reported by Cook *et al.*[2] The purpose of the present paper is to clarify this confusion in the literature.



I: X=Br
II: X=OH



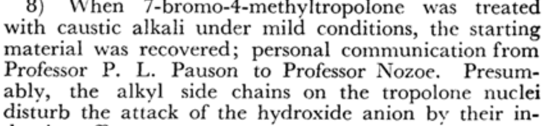
III



IV: X=OH
V: X=Br

The reaction of I with aqueous sodium hydroxide, when carried out according to Cook's procedure, led to the isolation of a single product which was shown to be identical with III by a comparison of their infrared and ultraviolet spectra and by a mixed-melting-point determination. Furthermore, a careful examination of the crude reaction product and mother liquor residues by means of infrared and ultraviolet spectroscopy did not show any evidence of the presence of II, even though II has very characteristic spectra[5,7] and its solubility is very different from that of III. When V was treated with aqueous potassium hydroxide under the same conditions[5] as more used for obtaining III from I, the starting material was recovered in a good yield.[8] Under more drastic conditions, the reaction afforded a single product (VI) in a poor yield and as colorless prisms, mp 179°C (molecular formula: $C_{10}H_{12}O_3$); no other crystalline substance was obtained. Compound VI, which has an ultraviolet spectrum very similar to that of III,[5] was also obtained when V was treated with sodium hydroxide under the reported conditions.[6] With thionyl chloride, VI gave an oil (VII) which has an ultraviolet spectrum typical of the tropones.[9]

When treated with diluted alkali, VII afforded white needles (VIII), $C_{10}H_{11}O_2Cl$, with an ultraviolet spectrum almost identical to that of *m*-chlorobenzoic acid.[5] The oxidation of VIII with nitric acid yielded a dibasic acid (IX) identical



VI VII VIII: X=isopropyl
IX: X=COOH

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1) T. Nozoe, Y. Kitahara and S. Masamune, *Proc. Japan Acad.*, **27**, 649 (1951).

2) B. J. Abadir, J. W. Cook, J. D. Loudon and D. K. Steel, *J. Chem. Soc.*, **1952**, 2350.

3) T. Nozoe and Y. Kitahara, *Proc. Japan Acad.*, **30**, 204 (1954).

4) Y. Kitahara, *Sci. Repts. Tohoku Univ. Ser. I*, **39**, 258 (1956).

5) Y. Kitahara, *ibid.*, **39**, 275 (1956).

6) Y. T. Lin, C. L. Chen and K. T. Wang, *J. Chinese Chem. Soc.*, **4**, 69 (1957).

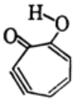
7) T. Nozoe, S. Seto, S. Ito, M. Sato and T. Katono, *Sci. Repts. Tohoku Univ. Ser. I*, **37**, 19 (1953).

8) When 7-bromo-4-methyltropolone was treated with caustic alkali under mild conditions, the starting material was recovered; personal communication from Professor P. L. Pauson to Professor Nozoe. Presumably, the alkyl side chains on the tropolone nuclei disturb the attack of the hydroxide anion by their inductive effects.

9) T. Nozoe, K. Takase and H. Matsumura, "Dai Yuki Kagaku," Vol. 13, Asakura Shoten, Tokyo (1960), p. 75, and the literature cited therein.

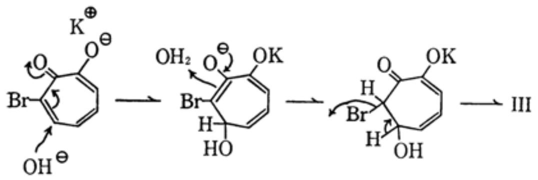
with 5-chloroisophthalic acid,[10] which had been synthesized from 5-nitroisophthalic acid.[11] Compound VI must, therefore, be 6-hydroxyhinokitiol,[12] while VIII is 3-chloro-5-isopropylbenzoic acid.

Although it is clear from the above that both I and its isopropyl derivative, V, afforded mainly abnormal substitution products when treated with caustic alkali, the mechanism of these reactions has not yet been established. In the literature there are two different opinions about the mechanism of this type of abnormal substitution reaction. A few years ago, Doi proposed a *benzyne*-type intermediate (X) for these reactions.[13]


X

However, as Kitahara *et al.*[14,15] pointed out, a *Michael*-type addition elimination mechanism could also explain these abnormal reactions.

Ring formation reaction at the C_4–C_5 positions of the tropolone nuclei in several tropolones[16-20] and abnormal substitution reactions at the C_7 position of 2-halo-tropones[21-28] and tropolone arylsulfonates[27,28] can be explained by a *Michael*-type addition elimination reaction mechanism,[4,15,16,18,20] but not by a mechanism involving the formation of a *benzyne*-type intermediate. From the considerations mentioned above, it seems preferable to explain the reactions of I and V with caustic alkali by a *Michael*-type addition elimination mechanism.



Experimental[29]

The reaction of I with 50% aqueous sodium hydroxide was carried out according to Cook's procedure.[2] From 2.00 g of I, 0.22 g of a crude crystalline substance was obtained; three recrystallizations from acetic acid then gave 0.17 g of colorless needles, mp 229—230°C; undepressed on admixture with III.[4] UV λ_{max}^{MeOH} mμ (log ε); 252 (4.59), 328 (3.73), 353 (3.77). IR KBr pellet; 3170, 3040, 2900—2500 (broad), 1590, 1575, 1470, 1418, 1341, 1277 (sh), 1270, 1207, 1183, 1050 (w), 985, 884, 807, 752 and 731 cm^{-1}. A second crop, 0.02 g of needles, mp 226.5—228°C, was also obtained. The UV and IR spectra of the residue obtained by evaporation of the mother liquor (0.02 g) were: UV λ_{max}^{MeOH} mμ (log ε); 251 (4.43), 328 (3.63), 355 (3.72). IR KBr pellet; 3170, 2900—2500 (broad), 1588, 1575, 1420, 1340, 1270, 1210, 1185, 985, 885, 805, 750 and 730 cm^{-1}.

6-Hydroxyhinokitiol (VI). A mixture of 1.20 g of V, 5.0 g of potassium hydroxide, and 2.0 m*l* of water was heated at 150°C (bath) for two hours in a hard glass tube. Since the mixture gradually turned into gummy mass, the mixture was stirred and ground continuously by means of a glass rod. Otherwise, the starting material would have been recovered. After cooling, the mixture was adjusted to about pH 4 with 2 N hydrochloric acid, then continuously extracted with ether until the water layer afforded no coloration with ferric chloride. The ether layer was washed with water, dried over sodium sulfate, filtered, and concentrated. The residue was sublimed under reduced pressure (1.5 mmHg) to give a pale yellow solid. Recrystallization of the sublimate from dilute methanol afforded 0.05 g of colorless prisms of VI, mp 177.5—179°C.

Found: C, 66.73; H, 6.68%. Calcd for $C_{10}H_{12}O_3$: C, 66.73; H, 6.71%. UV λ_{max}^{MeOH} mμ (log ε); 252 (4.54), 312 (shoulder), 353 (3.71). UV of the recrystallization residue; λ_{max}^{MeOH} mμ (log ε); 250 (4.50), 310 (sh), 355 (3.60). The same results were obtained when V was treated with 50% sodium hydroxide.[6]

3-Chloro-5-isopropylbenzoic Acid (VIII). A mixture of 0.05 g of VI, 0.5 m*l* of thionyl chloride, and 2.0 m*l* of anhydrous benzene was heated under reflux for five hours, then concentrated, poured into 10 m*l* of cold water, and extracted with petroleum ether for three times. The combined petroleum ether extracts were washed with water, dried over sodium sulfate, filtered, and evaporated under reduced pressure to give 0.03 g of a pale yellow oil; λ_{max}^{MeOH} mμ (log ε); 248 (4.27), 322 (3.70) as $C_{10}H_{10}OCl_2$. This oil was treated with 2 m*l* of 2 N sodium hydroxide on a water bath for two hours and then washed with ether. The aqueous layer was acidified with 2 N hydrochloric acid and extracted several times with ether. The combined ether layers were washed with water and dried over sodium sulfate, and the ether was removed under reduced pressure.

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[10] B. Baeyer, *J. Prakt. Chem.*, **25**, 506 (1882).
[11] R. Meyer and H. Wesche, *Ber.*, **50**, 442 (1917).
[12] VI was also synthesized by Doi from 6-aminohinokitiol; K. Doi, This Bulletin, **35**, 67 (1962).
[13] K. Doi, *ibid.*, **34**, 497 (1961).
[14] Y. Kitahara, *Sci. Repts. Tohoku Univ., Ser. I*, **39**, 250 (1956).
[15] Y. Kitahara, K. Doi and T. Kato, This Bulletin, **37**, 1744 (1964).
[16] K. Ogura, *ibid.*, **35**, 808 (1962).
[17] S. Seto, Y. Nishiyama and K. Ogura, *ibid.*, **35**, 1998 (1962).
[18] K. Ogura, *ibid.*, **36**, 45 (1963).
[19] S. Seto, K. Ogura and Y. Nishiyama, *ibid.*, **36**, 173 (1963).
[20] S. Seto and K. Ogura, *ibid.*, **37**, 1526 (1964).
[21] T. Nozoe, S. Seto and T. Sato, *Proc. Japan Acad.*, **30**, 476 (1954).
[22] T. Sato, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **80**, 1056, 1167, 1171, 1340 (1959).
[23] T. Nozoe, S. Seto, S. Matsumura and T. Asano, *Proc. Japan Acad.*, **32**, 339 (1956).
[24] T. Nozoe, S. Seto and S. Nozoe, *ibid.*, **32**, 472 (1956).
[25] S. Seto and S. Nozoe, *ibid.*, **32**, 765 (1956).
[26] T. Sato, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **80**, 1342 (1959).
[27] T. Sato, *ibid.*, **80**, 1058 (1959).
[28] T. Sato, *ibid.*, **80**, 1347, 1349 (1959).

[29] All melting points are uncorrected.

Recrystallization of the residue from petroleum ether (60—80°C) gave 0.015 g of colorless needles of VIII, mp 111—112°C; sinter at 105°C.

Found: C, 60.08; H, 5.69%. Calcd for $C_{10}H_{11}O_2Cl$: C, 60.44; H, 5.58%. λ_{max}^{MeOH} 285 mμ (log ε 3.10).

5-Chloroisophthalic Acid (IX). a) A solution of 0.06 g of VIII and 0.01 g of ammonium vanadate in 1.0 m*l* of 50% nitric acid was heated at 100°C for eight hours. On being allowed to cool, the reaction mixture deposited colorless needles which, after recrystallization from water, gave 0.04 g of colorless needles of IX, mp 277°C; a mixed-melting-poing determination with a synthetic specimen failed to show any depression.

Found: C, 44.55; H, 3.39%. Calcd for $C_8H_5O_4Cl \cdot H_2O$: C, 43.95; H, 3.27%. $C_8H_5O_4Cl \cdot {}^1/_2H_2O$: C, 45.86; H, 2.89%.[30]

b) A mixture of 0.02 g of 5-nitroisophthalic acid[11] and 0.10 g of 5% Pd on carbon in 20 m*l* of alcohol was shaken in a hydrogen atmosphere. After the absorption of three moles equivalent of hydrogen, the solution was filtered from the catalyst and concentrated. Recrystallization of the residue from alcohol afforded 0.15 g of micro needles of 5-aminoisophthalic acid, mp>300°C.

Found: N, 7.56%. Calcd for $C_8H_7O_4N$: N, 7.73%.

The amino acid (0.10 g) was diazotized in the usual way and stirred, and added drop by drop into an ice-cold solution of 1.0 g of cuprous chloride in 10.0 m*l* of concentrated hydrochloric acid. The solution was allowed to stand at room temperature for four hours and then warmed at 50°C for thirty minutes. The colorless precipitate which separated was recrystallized from water to give 0.08 g of colorless needles of IX, mp 277°C.

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[30] IX has been reported by Baeyer to have 1/2 H_2O.[10]