UDC 615.779.931-011

161. Zen-ichi Horii, Takefumi Momose, Masaori Naruse, and Yasumitsu Tamura : Studies on Oxytetracycline and Related Compounds. XVII.[1] Synthesis of 1,3,11-Trimethoxynaphthacenequinone.

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In the preceding paper,[1] it was reported that an attempt to prepare 1,3,11-trimethoxynaphthacenequinone (V) by oxidation of 1,3,11-trimethoxy-5(12*H*)-naphthacenone was unsuccessful. The present report describes the preparation and reduction of (V), as shown in Chart 1, as well as 1,3-dimethoxyanthraquinone (XIII) carried out as an exploratory experiment.

The Friedel-Crafts reaction of 3,5-dimethoxyphthalic anhydride (I)[2] with 1-naphthol employing aluminum chloride in tetrachloroethylene gave 2-(1-hydroxy-2-naphthoyl)-3,5-dimethoxybenzoic acid (II) and the corresponding pseudo keto-acid (III), whose structures were assigned by their infrared spectra.[3] The acid (II) was cyclized with conc. sulfuric acid containing a small amount of boric acid to 11-hydroxy-1,3-dimethoxynaphthacenequinone (IV). When the methyl ether (V) of (IV) was reduced with sodium hydrogensulfite in alkaline medium, it gave 1,3,11-trimethoxy-5(12*H*)-naphthacenone (VI), which was identical with a sample of (VI) obtained in the preceding paper.[1] Thus, the transformation from (I) to (IV) as stated above has also been proved.

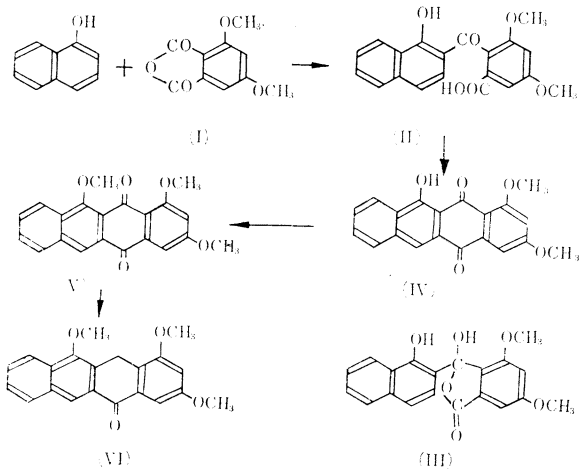

Chart 1.

α-(2,4-Dimethoxyphenyl)-*o*-toluic acid (X) was prepared by the reduction of *o*-(2,4-dimethoxybenzoyl)benzoic acid (VIII), according to the method of Scholl,[4] or by the reduction of *o*-(2,4-dihydroxybenzoyl)benzoic acid (VII) with zinc dust in sodium hydroxide

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1) Part XVI : This Bulletin. **10**, 946(1962).
2) H. Brockmann, F. Kluge, H. Muxfeldt : Chem. Ber., **90**, 2302 (1957).
3) W. Graf, E. Girod, E. Schmid W.G. Stoll : Helv. Chim. Acta, **42**, 1085 (1959); J.F. Grove, H.A. Willis : J. Chem. Soc., **1951**, 877; Z. Horii, Y. Tamura, K. Okumura, H. Kugita : Yakugaku Zasshi, **74**, 466 (1954).
4) C, Dufraisse, A. Allais, J. Robert : Bull. soc. chim. France, **1947**, 701; cf. R. Scholl : Ber., **44**, 1080 (1911).

solution, followed by methylation with dimethyl sulfate. The acid (X) was treated with phosphorus pentachloride in dry carbon disulfide to give the acid chloride, which was cyclized to 2,4-dimethoxyanthrone (XII) with aluminum chloride. In the presence of anhydrous stannic chloride, the anthrone (XII) was also prepared by the cyclization of acid chloride of α-(5-bromo-2,4-dimethoxyphenyl)-*o*-toluic acid (XI), which was obtained by bromination of (X) with bromine in chloroform. Thus, it was exemplified again that the displacement of bromine atom substituted in benzene nucleus with hydrogen occurred during the course of cyclization by the Friedel-Crafts method using stannic chloride.[1] The anthrone (XII) was oxidized with chromium trioxide in glacial acetic acid at room temperature to (XIII), reduction of which with sodium hydrogensulfite in alkaline medium gave (XII).

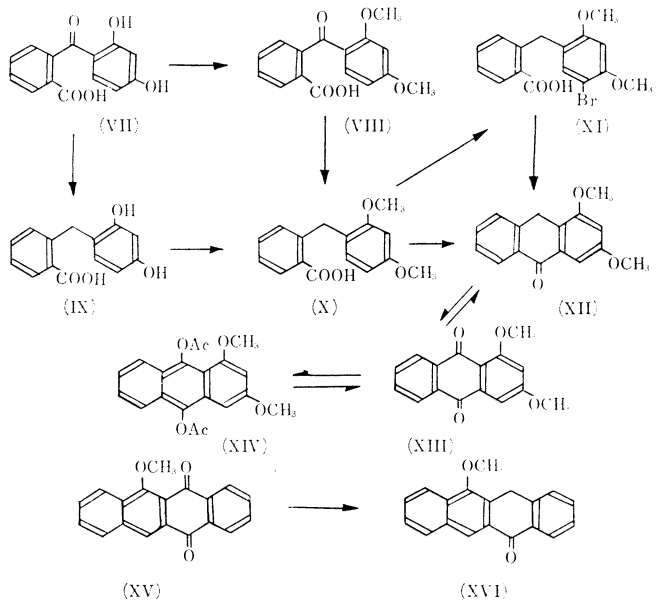

Chart 2.

Concerning to the reduction of anthraquinone derivatives having substituents, such as amino, hydroxyl and methoxyl groups[2,5~9] in the nucleus to the corresponding anthrone, it has been observed that the substituent, in co-operation with the reducing reagent employed, dominates the susceptibility of the quinone-carbonyl group to reduction. For example, reduction of amino-anthraquinone[5] with sodium hydrogensulfite in alkaline medium gives such an anthrone as a quinone-carbonyl group located at *meta*-position to the amino-substituent in anthraquinone is predominantly reduced, and reduction of methoxy- or hydroxyanthraquinone with an acidic reducing reagent such as hydriodic acid[8] or stannous chloride-hydrochloric acid[9] gives an anthrone which has a hydroxyl substituent at *peri*-position to the anthrone-carbonyl group. In the present experiment, treatment of (V), (XIII) and 6-methoxynaphthacenequinone (XV) with sodium hydrogensulfite in alkaline medium resulted in a reduction of the carbonyl group located

5) W, Bradley, R.F. Maisey : J. Chem. Soc., **1954**, 274.
6) H. Brockmann, R. Neff, E. Mühlmann : Chem. Ber., **83**, 467 (1950).
7) J.W. Cook, P.L. Pauson : J. Chem. Soc., **1949**, 2726.
8) Yao-Tsêng Huang : Tetrahedron, **11**, 52 (1960).
9) G.F. Atree, A.G. Perkin : J. Chem. Soc., **1931**, 144.

at *peri*-position to the methoxyl group to give (VI), (XII) and 11-methoxy-5(12*H*)-naphthacenone (XVI), respectively, as mentioned above. However, reduction of (V) and (XIII) with stannous chloride-hydrochloric acid in acetic acid gave no crystalline product, although Attree and Perkin[9] reported the formation of 1,3-dihydroxyanthrone from (XIII) by the same reductive method.

Experimental

3,5-Dimethoxyphthalic Anhydride (I)——(I) was prepared from 3,5-dihydroxybenzoic acid[10] according to the procedure of Brockmann, Kluge and Muxfeldt.[2]

2-(1-Hydroxy-2-naphthoyl)-3,5-dimethoxybenzoic Acid (II)——To a solution of 9.3 g. of (I) and 10 g. of 1-naphthol in 60 ml. of tetrachloroethylene was added 7.2 g. of pulverized anhyd. $AlCl_3$ in one portion and the mixture was stirred for 1 hr. at room temperature and then for 30 min. at 100°. The reaction mixture was poured into ice-conc. HCl and subjected to steam-distillation. The dark brownish half solid was separated from the residue by decanting the aqueous layer while hot, and dissolved in hot Na_2CO_3 solution. The alkaline solution was acidified with conc. HCl, and it gave 8.5 g. of crude product, which (6.2 g.) was extracted several times with hot benzene. The benzene-insoluble material was recrystallized from MeOH to 2.8 g. of (II), m.p. 235~238°, light yellow crystals. $FeCl_3$-test : dark green. *Anal.* Calcd. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found : C, 68.32; H, 4.54. IR ν_{max}^{Nujol} cm^{-1} : 2632 (OH), 1689 (COOH), 1630 (CO).

The benzene solution was evaporated and the residue was recrystallized from EtOH to 2.4 g. of the pseudo keto-acid (III) corresponding to (II), m.p. 172~177°, yellow needles. An analytical sample, m.p. 180~181°, was prepared by repeated recrystallization from EtOH. $FeCl_3$-test : dark green. *Anal* Calcd. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found : C, 68.53; H, 4.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3350 (OH), 1727 (CO).

Another preparation in nitrobenzene gave less yield.

11-Hydroxy-1,3-dimethoxynaphthacenequinone (IV)——A mixture of 1 g. of H_3BO_3 and 10 ml. of conc. H_2SO_4 was heated until a clear solution resulted. To this, 1 g. of the acid (II) was added and the mixture was heated at 120~125° for 10 min.*2 Initial reddish brown color of the mixture turned into deep bluish purple during the reaction. The reaction mixture was poured into ice-water, and the red deposits were collected and dried. The dried product was dissolved in hot benzene, which was followed to keep standing overnight, giving 200 mg. of red crystals. This crude crystals (120 mg.) were chromatographed through silica-gel column with $CHCl_3$ as eluent. Elution of the deep red band gave 89 mg. of orange-red crystals, which gave red needles, melting at 239~240° by three recrystallizations from benzene. $FeCl_3$-test : brown in EtOH. *Anal.* Calcd. for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found : C, 72.02; H, 3.86. IR ν_{max}^{Nujol} cm^{-1} : 1656, 1608 (CO).

1,3,11-Trimethoxynaphthacenequinone (V)——A suspension of 200 mg. of the crude quinone (IV) and 100 mg. of KOH in 20 ml. of dehyd. MeOH was refluxed for 15 min. and the solvent was removed in a reduced pressure. The residue was added to a mixture of 15 g. of MeI, 2 g. of anhyd. K_2CO_3 and 20 ml. of dehyd. Me_2CO and they were refluxed for 6 hr. Further, 15 g. of MeI, 2 g. of anhyd. K_2CO_3 and 5 ml. of dehyd. Me_2CO were added to the reaction mixture, which was refluxed for additional 9 hr. Color of the mixture turned from deep purple-red to light yellow. Inorganic salts separated were removed by filtration and the filtrate was evaporated to give 900 mg. of residue, which was recrystallized from Me_2CO to 150 mg. of light yellow needles, m.p. 219~221°. *Anal.* Calcd. for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63. Found : C, 72.27; H, 4.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1661 (CO).

1,3,11-Trimethoxy-5(12*H*)-naphthacenone (VI)——To a solution of 100 mg. of (V) in hot MeOH, a solution of 1 g. of $Na_2S_2O_4$ and 0.5 g. of NaOH in 15 ml. of H_2O was added and the mixture was refluxed for 50 min. The pale purple solution thus obtained was poured into 5 volumes of H_2O. The crystals precipitated were washed with H_2O and recrystallized from H_2O-Me_2CO, giving 18 mg. of colorless (VII), m.p. 179~181°. This was identical with a sample of (VII) prepared in the preceding report[1] by a comparison of their IR spectra. *Anal.* Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found : C, 75.22; H, 5.15.

*2 The following coloration test is recommended to determine an optimal reaction time. A small portion of the reaction mixture was taken up, diluted with H_2O and shaken with AcOEt. If the reaction time employed is proper, an aqueous layer would not give any coloration. When the reaction was taken place either in the prolonged time or at higher temperature, the aqueous layer would give red coloration, which is presumably ascribed to the formation of sulfonated naphthacene derivatives.

10) A. W. Weston, C. M. Suter : Org. Syntheses, Coll., Vol. III, p. 288 (1955).

α-(2,4-Dimethoxyphenyl)-*o*-toluic Acid (X)——i)[4] Prepared from *o*-(2,4-dihydroxybenzoyl)benzoic acid (VII)[11] through the corresponding dimethyl ether (VIII).[12]

ii) To a mixture of 20 g. of (VII), 30 g. of KOH, 100 ml. of H_2O and 30 g. of Zn-dust, a solution of 1 g. of $CuSO_4 \cdot 5H_2O$ in 5 ml. of 28% NH_4OH was added, and the mixture was refluxed for 5 hr. The reaction mixture was acidified with ice-20% H_2SO_4 and extracted with AcOEt. The extract was shaken with saturated Na_2CO_3 solution, the aqueous layer was acidified with 20% H_2SO_4 and re-extracted with AcOEt. The AcOEt solution washed with H_2O, dried over Na_2SO_4 and evaporated to give 22.2 g. of solid. Trituration of the solid with benzene gave pale yellow prisms (IX), m.p. 141~143° (Lit., 143°[11]).

To a stirred solution of 8.8 g. of (IX) and 27.2 g. of Me_2SO_4 in 20 ml. of MeOH, a mixture of 30 g. of KOH and 30 ml. of H_2O was added dropwise within 1 hr., and the mixture was heated on a steam bath for additional 1 hr. The cooled reaction mixture was diluted with 5 volumes of H_2O, acidified with ice-20% H_2SO_4 and extracted with AcOEt. The AcOEt extract was shaken with Na_2CO_3 solution, the aqueous layer was acidified and re-extracted with AcOEt, which was washed again with H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from aq. EtOH to give 6.5 g. of crystals, m.p. 145~148°, which was identical with a sample of (X) obtained in i) by mixed melting point determination.

α-(5-Bromo-2,4-dimethoxyphenyl)-*o*-toluic Acid (XI)——To an ice-cooled solution of 1.2 g. of (X) in 40 ml. of $CHCl_3$, 0.75 g. of Br_2 was added dropwise. After a complete addition, the mixture was stirred for additional 30 min. The $CHCl_3$ layer was washed with 10% Na_2CO_3 and the aqueous layer was acidified with conc. HCl. The precipitates were washed with H_2O and recrystallized from either AcOEt or EtOH to afford slightly brown-colored needles, m.p. 165~168°. Yield, 66%. *Anal.* Calcd. for $C_{16}H_{15}O_4Br$: C, 54.73; H, 4.28; Br, 22.76. Found: C, 54.56; H, 4.13; Br, 22.98.

2,4-Dimethoxyanthrone (XII)——i) From (X): To an ice-cooled stirred solution of the acid chloride (prepared from 2.5 g. of (XI) employing 2.0 g, of PCl_5 in 50 ml. of dehyd. CS_2), 1.5 g. of anhyd. $AlCl_3$ was added in small portions and the mixture was stirred for 10 min. at room temperature, for 15 min. at 40~45° and then for 15 min. at 60°. The cooled mixture was poured into ice-10% H_2SO_4 and extracted with AcOEt, which was washed with saturated $NaHCO_3$ solution and then H_2O, dried and evaporated, giving 2.4 g. of dark brown half-solid, which was crystallized from Me_2CO to 500 mg. of pale yellow plates, m.p. 209~212°. An analytical sample, m.p. 210~212°, was prepared by two recrystallizations from Me_2CO. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 75.57; H, 5.55. Found: C, 75.22; H, 5.46. IR: $\nu_{max}^{CHCl_3}$ cm^{-1} 1706, 1658 (CO).

ii) From (XI): (XI) (600 mg.) was refluxed with 450 mg. of PCl_5 in 45 ml. of dehyd. benzene for 10 min. To the resulting solution, a solution of freshly distilled anhyd. $SnCl_4$ (6 ml.) in 6 ml. of dehyd. benzene was added, and the mixture was stirred for 10 min. at 10~15° and then for 5 min. at 50°. After rapid cooling, the mixture was treated with ice-10% H_2SO_4, the organic layer was separeted and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with saturated $NaHCO_3$ solution and then H_2O, dried and evaporated, giving 200 mg. of pasty residue. The residue was extracted with Et_2O which was evaporated. Recrystallization of the residue from Me_2CO gave pale yellow platelets of m.p. 208~210.5°. This compound sublimed at 205~210°, showed a negative Beilstein-test and was identical with a sample of (XII) prepared in i). From the $NaHCO_3$ washings, 180 mg. of the starting material (XI) was recovered.

iii) Reduction of (XIII) with $Na_2S_2O_4$ in alkaline medium: A mixture of 93 mg. of (XIII), 1 g. of $Na_2S_2O_4$, 0.5 g. of NaOH, 10 ml. of MeOH and 10 ml. of H_2O was refluxed for 3 hr. After diluted with H_2O, the mixture was extracted with AcOEt, which was washed with H_2O, dried and evaporated. The residue (100 mg.) was triturated with benzene and the resulting crystals were recrystallized from aq. Me_2CO, giving 12 mg. of yellow crystals, m.p. 205~208°, which was identical with a sample of (XII) prepared in i) and ii). Uncrystallizable fraction was chromatographed through siliga-gel column with $CHCl_3$ as eluant, giving 40 mg. of (XII) and 10 mg. of the starting material (XIII).

1,3-Dimethoxyanthraquinone (XIII)——To a stirred solution of 250 mg. of (XII) in 10 ml. of glacial AcOH freshly distilled over $KMnO_4$, 200 mg. of CrO_3 in 10 ml. of the same AcOH was added at room temperature and was continued to the stirring for further 24 hr. The mixture was poured into 10 volumes of H_2O and the yellow crystals deposited were collected. Recrystallization from aq. MeOH gave yellow needles, m.p. 162.5~163.5°. *Anal.* Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 72.03; H, 4.58. IR: $\nu_{max}^{CHCl_3}$ cm^{-1} 1661 (CO).

1,3-Dimethoxy-9,10-anthracenediol Diacetate (XIV)——A mixture of 138 mg. of the quinone (XIII), 100 mg. of anhyd. AcONa, 900 mg. of Zn-dust and 50 ml. of Ac_2O was refluxed for 1 hr. and then poured into 100 ml. of H_2O. It was extracted with benzene and the extract was washed successively

11) R.D. Desai and F. Figueredo: Proc. Indian Acad. Sci., **14A**, 605 (1941).

12) J.D. Reinheimer, C.R. Bresson, A.J. Holloway and C.R. Dailey: J. Am. Chem. Soc., **77**, 1909 (1955); W.R. Orndorf, E. Kline: *Ibid.*, **46**, 2287 (1925); cf. T. Tambor: Ber., **43**, 1886 (1910).

with $NaHCO_3$ solution and H_2O, dried Na_2SO_4 and evaporated, giving 150 mg. of paste, which was solidified on standing. The solid was washed with Et_2O and the resulting yellow crystals (100 mg.) with fluorescence were recrystallized from MeOH and then from H_2O-Me_2CO, m.p. 200~202°. *Anal.* Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found : C, 67.67; H, 5.20. IR : $\nu_{max}^{CHCl_3}$ cm^{-1} 1759($OCOCH_3$), 1629.

The diacetate was reconverted to (XIII) by alkaline hydrolysis with KOH solution in a quantitative yield.

6-Methoxynaphthacenequinone (XV)[13]——A suspension of 100 mg. of 6-hydroxynaphthacenequinone and 50 mg. of KOH in 10 ml. of MeOH was refluxed for 15 min. and evaporated to dryness in a reduced pressure. The residue was added to a mixture of 1 g. of anhyd. K_2CO_3, 10 g. of MeI and 20 ml. of dehyd. Me_2CO, and the mixture was refluxed for 13 hr. During the reaction, initial deep red-purple color of the reaction mixture turned to pale yellow. Inorganic salts were removed by filtration and the filtrate was evaporated. The resulting residue was crystallized from EtOH or Me_2CO to give 100 mg. of light yellow needles, m.p. 210~212°(Lit., 210°[13]). IR : $\nu_{max}^{CHCl_3}$ cm^{-1} 1672(CO).

11-Methoxy-5(12*H*)-naphthacenone (XVI)——To a solution of 100 mg. of (XV) in 10 ml. of MeOH a solution of 1 g. of $Na_2S_2O_4$ and 0.5 g. of NaOH in 10 ml. of H_2O was added. The resulting dark green mixture was refluxed for 20 min., giving a pink-colored clear solution. The solution was poured into 20 ml. of H_2O and the colorless crystals deposited (62 mg.) were recrystallized from H_2O-Me_2CO, m.p. 175°. *Anal.* Calcd. for $C_{19}H_{14}O_2$: C, 83.20; H, 5.15. Found : C, 82.95; H, 5.01. IR : $\nu_{max}^{CHCl_3}$ cm^{-1} 1653(CO).

Summary

1,3,11-Trimethoxynaphthacenequinone (V) and 1,3-dimethoxyanthraquinone (XIII) were prepared as shown in Charts 1 and 2. Reduction with sodium hydrogensulfite in alkaline medium converted the quinones, (V), (XIII) and 6-methoxynaphthacenequinone (XV), to 1,3,11-trimethoxy-5(12*H*)-naphthacenone (VI), 2,4-dimethoxyanthrone (XII) and 11-methoxy-5(12*H*)-naphthacenone (XVI), respectively.

(Received November 16, 1961)

13) Cf. G. Wolf : J. Am. Chem. Soc., **75**, 2673 (1953).

UDC 615.786[612.741.15]-011

162. Tokuji Suzuki : Studies on Decomposition and Stabilization of Drugs in Solution. XI.*1 Chemical Kinetic Studies on Aqueous Solution of Succinylcholine Chloride. 3. Overall Velocity Constants for Succinylmonocholine Chloride Hydrolysis as a Function of pH.

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In the preceding paper,[1] velocity constants of hydrolysis of succinylcholine chloride (I) could be shown for over the whole pH range of 0.9 to 8.5 by using ion exchange chromatography method. From the literature,[2] the degradation of (I) in aqueous solution may be represented in the following manner.

*1 This work constitutes a part of a series entitled "Studies on Decomposition and Stabilizaion of Drugs in Solution" by H. Nogami. Part X : This Bulletin, **10**, 912(1962).

*2 Hongo, Tokyo (鈴木徳治).

1) T. Suzuki : This Bulletin, **10** 912(1962).

2) V.P. Whittaker : Experientia, **7**, 251 (1951).