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Chemical Studies on the Natural Anthraquinones. I.[1] Synthesis of Munjistin, Emodin and 3-Hydroxy-2-methylanthraquinone

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In the previous paper[1b] it had been reported that 1,3-dihydroxy-2-anthraquinonecarboxylic acid (I) synthesized through 1,4-dihydroxy-2-methylanthraquinone (II) was identical with natural munjistin.

The present paper deals with the another simplified synthesis of I, emodin (1,6,8-trihydroxy-3-methylanthraquinone[3]) (III) and 3-hydroxy-2-methylanthraquinone (IV), the one of components of *Coprosma lucida*.[4]

1) (1) Synthesis of I from Resorcinol Dimethyl Ether (V) and Monomethyl Ether (VI)——It had been known that the condensation with phthalic anhydride (VII) and resorcinol (VIII) by zinc chloride and sulfuric acid gave fluorescein, namely 3,3-di(2,4-dihydroxyphenyl)-phthalide (IX).[5] But the condensation with VII and V by anhydrous aluminum chloride was attempted with the reaction temperature at 110° for 6 hr and at $<70°$ for 6 hr to give product A ($C_{15}H_{12}O_5$) and B ($C_{24}H_{22}O_6$) respectively. Product A was shown to be 2-(2-hydroxy-4-methoxybenzoyl)benzoic acid (X) which was confirmed by infrared (IR) spectrum as described in experimental, and also obtained from the condensation with VII and VI. Product B showed the band of 1762 cm^{-1} indicative a carbonyl stretching due to a five membered lactone in IR spectrum, and the signals of singlet, 6.47 and 6.21 τ indicative six protons of methoxyl groups in nuclear magnetic resonance (NMR) spectrum respectively. Therefore product B was shown by formula 3,3-di(2,4-dimethoxyphenyl)phthalide (XI). Compound X was ringclosured by a molten mixture of anhydrous aluminum chloride and sodium chloride to be converted to 1,3-dihydroxyanthraquinone (XII) which was proved by comparing with the authentic sample. Synthesis of I starting from XII had been reported.[6]

(2) Synthesis of I from 1,2-Dihydroxyanthraquinone (XIII)——C-3 of XIII was substituted with formyl group by hexamethylenetetramine to be converted to 1,2-dihydroxy-3-anthraquinonecarbaldehyde (XIV) which was confirmed by IR spectrum showing the bands indicative a non-chelated quinone (1668 cm^{-1}), a chelated quinone (1645 cm^{-1}) and a chelated aldehyde (1650 cm^{-1}). Oxidation of XIV with manganese dioxide followed by reduction with sodium dithionate gave 1,3-dihydroxy-2-anthraquinonecarbaldehyde (XV) which was confirmed by comparing with the authentic sample.[6] Consequently, the former reaction product was shown by formula 1,2,4-trihydroxy-3-anthraquinonecarbaldehyde (XVI). Synthesis of I from XV had been reported.[6]

1) *a*) This report forms "Studies on the Synthesis of Munjistin. V," by Y. Hirose; *b*) Part IV: Y. Hirose, J. Kusuda, S. Nonomura and H. Fukui, *Chem. Pharm. Bull.* (Tokyo), **16**, 1377 (1968).
2) Location: *Oe-Moto-Machi, Kumamoto.*
3) *a*) H. Brockmann, F. Kluge, and H. Muxfeldt, *Chem. Ber.*, **90**, 2302 (1957); *b*) R.A. Jacobson and R. Adams, *J. Am. Chem. Soc.*, **46**, 1312 (1924).
4) L.H. Briggs and G.A. Nicolls, *J. Chem. Soc.*, **1949**, 1241.
5) *a*) Gattermann-Wieland, "Die Praxis des Organischen Chemikers," 40 Aufl. Walter de Gruyter & Co., Berlin, 1961, p. 282; *b*) A. Baeyer, *Ann.*, **183**, 3 (1876).
6) Y. Hirose, *Chem. Pharm. Bull.* (Tokyo), **10**, 985 (1962).

(3) Synthesis of I from 1,2-Diacetoxy-3-acetoxymethyl-4-hydroxyanthraquinone (XVII)[7] ——Compound XVII was methylated and saponified to be converted to 1,2-dihydroxy-3-hydroxymethyl-4-methoxyanthraquinone (XIX) which was reduced by sodium dithionate to be converted to 3-hydroxy-2-hydroxymethyl-1-methoxyanthraquinone (XX) being confirming by comparing with the authentic sample.[8] Convertion to I from XX had been reported.[8,9] On this occasion, the preparation of 2-acetoxy-3-acetoxymethyl-1,4-di-hydroxyanthraquinone (XXII) was described in experimental.

2) Synthesis of III

Synthesis of III had been reported by Brokmann, *et al.*[3a] and Adams, *et al.*[3b] In this paper synthesis of III was undertaken with another course. 3,5-Dimethoxy-2-(4-methyl-2-methoxybenzoyl)benzoic acid (XXIII) was prepared by methylation of the crude product yielded by Friedel-Crafts condensation with methyl 3,5-dimethoxybenzoate (XXIV) and 2-methoxy-4-methylbenzoic chloride (XXV). Cyclization of XXIII using a molten mixture of anhydrous aluminum chloride and sodium chloride gave exclusively III which was confirmed by comparing with the authentic sample.

3) Synthesis of IV

(1) The direct condensation of 3-methoxy-4-methylbenzoic acid (XXVI) and benzoic acid (XXVII) with sulfuric acid at 120° gave IV, mp >300°, 25% yield, and 1-hydroxy-2-methylanthraquinone (XXVIII), mp 177°. (lit.,[10] mp 177°, 7% yield). (2) Baeyer and Fraude[11] had reported that IV obtained by the condensation of *o*-cresol (XXIX) and VII with sulfuric acid melted at 262°. This condensation was reexamined, and established to afford IV, mp >300°, 27% yield and XXVIII, mp 177°, 11% yield. (3) It was established that the condensation of VII and *o*-cresol methyl ether (XXX) with anhyd. aluminum chloride at <70° gave exclusively 2-(4-methoxy-3-methylbenzoyl)benzoic acid (XXXI), and that the ringclosure of both XXXI and 2-(4-hydroxy-3-methylbenzoyl)benzoic acid (XXXII)[12b] using a molten mixture of anhyd. aluminum chloride and sodium chloride at 170° gave exclusively IV.[13] The product described in 13*a*) and *b*) as 2-hydroxy-1-methylanthraquinone (XXXIII),[12] mp >300°, being reexamined on this occasion, was confirmed to be IV, mp >300°.

Experimental

2(2-Hydroxy-4-methoxybenzoyl)benzoic Acid (X)——a) To a stirred solution of VII (5 g) in $CHCl_2$-$CHCl_2$ (200 ml) was added anhyd. $AlCl_3$ (15 g) in small portions, and then dropwise V (20 ml) at room temperature. The reaction temperature was maintained at room temperature for 12 hr, raised to 110° during 1 hr and kept for 6 hr with continuous stirring. The reaction mixture was poured on ice and dil. HCl, and steam-distilled to remove excess V and $CHCl_2CHCl_2$. The residue was extracted with ether. Ether extract was washed with 5% Na_2CO_3 which was acidified with dil. HCl. The deposited precipitate was recrystallized from EtOH to give 3.2 g (34% yield) of X, mp 163—164°, colorless needles. *Anal.* Calcd. for $C_{15}H_{12}O_5$: C, 66.73; H, 4.44. Found: C, 66.22; H, 4.20. IR ν_{max}^{KBr} cm^{-1}: 1690 ($-COO^-$), 1625 (C=O, chelated to 2-OH).

b) To a stirred mixed solution of VII (5 g) and anhyd. $AlCl_3$ (15 g) in $CHCl_2CHCl_2$ (200 ml) was added dropwise VI (20 ml) at room temperature. The treatment was carried out as in a) to give X, 49% yield, which was proved to be identical with the foregoing product X comparing their IR spectrum and mp.

3,3-Di(2,4-dimethoxyphenyl)phthalide (XI)——To a stirred solution of VII (5 g) and anhyd. $AlCl_3$ (15 g) in $CHCl_2CHCl_2$ (200 ml) was added dropwise V (20 ml) at room temperature. The reaction temperature was

7) Y. Hirose, *Chem. Pharm. Bull.* (Tokyo), **11**, 533 (1963).
8) Y. Hirose, *Chem. Pharm. Bull.* (Tokyo), **8**, 417 (1960).
9) S. Nonomura, *Yakugaku Zasshi*, **75**, 225 (1955).
10) R. Eder, C. Widmer, and R. Bütler, *Helv. Chim. Acta.*, **7**, 353 (1924).
11) A. Baeyer and G. Fraude, *Ann.*, **202**, 163 (1880).
12) *a*) W.H. Bentley, H.D. Gardner, and C. Weizmann, *J. Chem. Soc.*, **91**, 1631 (1907); *b*) F. Ullmann and W. Schmidt, *Ber.*, **52**, 2098 (1919).
13) *a*) C. Marschalk, *Bull. Soc. Chim.*, [5], **6**, 655 (1939)[*C.A.*, 33, 5388 (1939)]; *b*) P.C. Mitter and A.K. Sen, *J. Indian Chem. Soc.*, **5**, 631 (1928): *idem*, *Chem. Zentr.*, **1929**, 1105.

maintained at room temperature for 12 hr, raised to 70° during 1 hr and kept for 6 hr with continuous stirring. The reaction mixture was poured on ice and dil. HCl, and steam-distilled to remove excess V and $CHCl_2$-$CHCl_2$. The residue was alkalined with 1N NaOH cooling in ice water. The insoluble solid washed with H_2O was recrystallized from acetone to give colorless plates, mp 145°, 36.8% yield. *Anal.* Calcd. for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 70.48; H, 5.46. IR ν_{max}^{KBr} cm^{-1}: 1762 (five membered lactone C=O). NMR ($CDCl_3$) τ: 6.47 (3H×2, $-OCH_3$), 6.21 (3H×2, $-OCH_3$).

1,3-Dihydroxyanthraquinone (XII)——To a stirred molten mixture of anhyd. $AlCl_3$ (10 g) and NaCl (1 g) was added X (0.5 g) in small portions at 140—150°. The reaction temperature was raised to 160°, and maintained for 1.5 hr with continuous stirring. After cooling, the melt mass was poured on ice and dil. HCl, and allowed to stand overnight. The resulting precipitate was extracted with benzene. Benzene extract was shaken with 5% Na_2CO_3. The Na_2CO_3 phase was acidified with dil. HCl to precipitate 0.3 g (60% yield) of XII which was recrystallized from acetone in yellow needles, mp 268°. *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 70.00; H, 3.33. Found: C, 69.80; H, 3.40. IR ν_{max}^{KBr} cm^{-1}: 3380 (–OH), 1675 (C=O free), 1635 (C=O chelated).

1,2-Dihydroxy-3-anthraquinonecarbaldehyde (XIV)——A solution of XIII (1 g), hexamethylenetetramine (2 g) and AcOH (75 ml) was refluxed for 8 hr. After cooling, 24% HCl (40 ml) was added to the foregoing solution. The whole was heated on a steam bath for 1 hr and diluted with H_2O (400 ml) to be stood overnight. The resulting precipitate was repeatedly extracted with benzene of each 50 ml. The concentrated benzene extract was submitted to $CaHPO_3$ column chromatography developing with benzene. The deep brown coloring solid obtained from the most polar, intensely red band was sublimed at 220—230°/5 mm, and recrystallized from acetone to give 0.2 g of XIV, yellowish brown needles, 18% yield. *Anal.* Calcd. for $C_{15}H_8O_5$: C, 67.17; H, 3.01. Found: C, 67.10; H, 2.75. IR ν_{max}^{KBr} cm^{-1}: 1672 (C=O) non-chelated), 1650 (C=O chelated to 2-OH), 1645 (C=O chelated to 1-OH), 1592 (phenyl).

1,2,4-Trihydroxy-3-anthraquinonecarbaldehyde (XVI)——To a stirred solution of XIV (2 g) and 100% H_2SO_4 (40 ml) was added MnO_2[14] in small portions cooling at <0°. The reaction mixture was maintained at <0° for 3 hr with continuous stirring. The whole was poured on ice water (400 ml) and allowed to stand overnight. The black precipitate was shaken with 5% $NaHSO_3$ (100 ml). The filtered $NaHSO_3$ solution was acidified with 5% HCl (200 ml). The deep red, deposited precipitate was recrystallized from hexane to give red needles, mp 253° (decomp.), 0.6 g, 30% yield. *Anal.* Calcd. for $C_{15}H_8O_6$: C, 63.39; H, 2.84. Found: C, 63.82; H, 2.70. IR ν_{max}^{KBr} cm^{-1}: 1654 (C=O chelated to 2-OH), 1628 (C=O chelated to 1- and 4-OH), 1588 (phenyl).

1,3-Dihydroxy-2-anthraquinonecarbaldehyde (XV)——To a stirred solution of XVI (0.5 g) and 2% NaOH (100 ml) was added dropwise 5% $Na_2S_2O_4$ (30 ml) on a steam bath until the color of the reaction solution changed from red to yellow brown. Subsequently, 5% HCl (50 ml) was added dropwise to the foregoing mixture cooling in ice water when brown crystallines appeared. The obtained brown crystallines were recrystallized from acetone to give orange yellow needles, XV, mp 221—222°, 60% yield. Compound XV was identical with the authentic sample, nor-damnacanthal[7] comparing their IR spectrum and mp. *Anal.* Calcd. for $C_{15}H_8O_5$: C, 67.17; H, 3.01. Found: C, 67.00; H, 2.98, IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O non-chelated), 1645 (C=O chelated to 2-OH), 1630 (C=O chelated,) 1590 (phenyl).

1,2-Diacetoxy-3-acetoxymethyl-4-methoxyanthraquinone (XVIII)——A mixture solution of XVII (0.5 g), Ag_2O (1.5 g) and acetone (200 ml) was refluxed for 20 hr. Working up as usual, the obtained crude product was submitted to $CaHPO_3$ column chromatography developing with benzene. The benzene developer obtained from the most polar, intensely yellow broad band was washed with 1% NaOH followed with 3% HCl and with H_2O to be concentrated. The obtained residue was recrystallized from MeOH to give yellow needles, mp 152—154°. *Anal.* Calcd. for $C_{22}H_{18}O_9$: C, 61.97; H, 4.26. Found: C, 61.78; Y, 4.08. IR ν_{max}^{KBr} cm^{-1}: 1785 (phenol acetate), 1740 (alcohol acetate), 1675 (C=O non-chelated), 1594 (phenyl).

3-Hydroxy-2-hydroxymethyl-1-methoxyanthraquinone (XX)——A solution of XVIII (0.5 g) and 2% NaOH (100 ml) was heated on a steam bath to be dissolved for 1 hr. To this stirred solution heating on a steam bath was added dropwise 5% $Na_2S_2O_4$ (30 ml) until the color of the reaction solution changed from violet to brown. Subsequently, 5% HCl (90 ml) was added dropwise cooling in ice water when brown crystallized from acetone to give bright yellow needles, mp>300° (decomp.), 35% yield, which was identical with the authentic sample comparing their IR spectrum and mp. *Anal.* Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.42; H, 4.04.

2-Acetoxy-3-acetoxymethyl-1,4-dihydroxyanthraquinone (XXII)——A suspension of 1,2,4-trihydroxy-3-hydroxymethylan-thraquinone (XXI) (1 g)[7], $B(OAc)_3$[15] (2 g) prepared freshly and Ac_2O (50 ml) was warmed on a steam bath at 40—50° for 8 hr, and poured on water (400 ml). The resulting precipitate was recrystallized from AcOH to give red needles, mp 197—199°, 50% yield. *Anal.* Calcd. for $C_{19}H_{14}O_8$: C, 61.62; H, 3.78. Found: C, 61.68; H, 3.78. IR ν_{max}^{KBr} cm^{-1}: 1778 (phenyl acetate), 1745 (alcohol acetate), 1628 (C=O chelated), 1590 (phenyl).

14) J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, and T. Walker, *J. Chem. Soc.*, **1952**, 1094.
15) A. Pictet and A. Geleznoff, *Ber.*, **36**, 2219 (1903).

3,5-Dimethoxy-2(4-methyl-2-methoxybenzoyl)benzoic Acid (XXIII)——To a stirred solution of XXIV (6 g) and anhyd. $AlCl_3$ (10 g) in $CHCl_2CHCl_2$ (100 ml) was added dropwise a solution of XXV (5 g) and $CHCl_2$-$CHCl_2$ (100 ml) cooling in ice water. After adding, the reaction temperature was maintained at room temperature for 24 hr under continuous stirring. The reaction mixture was poured on ice and dil. HCl. and steam-distilled to remove $CHCl_2CHCl_2$. The residue was extracted with ether. Ether extract was washed with H_2O, dried and concentrated. A solution of the deposited crude solid, Me_2SO_4 (10 ml), anhyd. K_2CO_3 (20 g) and acetone (200 ml) was refluxed for 5 hr. The whole was filtered, the filtrate concentrated, and the residue heated with 2N NaOH (200 ml) on a steam dath for 1 hr. After cooling, the whole was acidified with dil. HCl. The resulting precipitate was recrystallized from MeOH to give colorless plates, mp 219° (*loc. cit.* in 3*a*, *b*), mp 219°), 25% yield. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 64.85; H, 5.45. IR ν_{max}^{KBr} cm^{-1}: 1690 ($-COO^-$), 1650 (C=O).

Emodin (1,6,8-Trihydroxy-3-methylanthraquinone) (III)——To a stirred molten mixture of anhyd. $AlCl_3$ (10 g) and NaCl (2 g) was added XXIII (91 g) in small portions at 120°. After adding, the reaction temperature was raised to 160°, and maintained for 0.5 hr with continuous stirring. After cooling, the melt was poured on ice and dil. HCl, and allowed to stand over night. The resulting precipitate was submitted to $CaHPO_3$ column chromatography developing with benzene. The benzene developer obtained from the most polar, intensely red broad band was concentrated. The resulting residue was recrystallized from acetone to give orange red needles, mp 254—256°, 49% yield, which was identical with the authentic sample comparing their IR spectrum and mp. *Anal.* Calcd. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73. Found: C, 66.94; H, 3.73. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O non-chelated), 1618 (C=O chelated).

3-Hydroxy-2-methylanthraquinone (IV) and 1-Hydroxy-2-methylanthraquinone (XXVIII)——a) A stirring mixture of XXVI (3 g), XXVII (4 g) and conc. H_2SO_4 (100 ml) was heated at 120° for 10 hr. The whole was poured on ice water and steam-distilled to deposit yellow crystallines in the steam-distillate, which was recrystallized from acetone to give bright yellow needles, XXVIII, mp 175—177°, 7% yield. *Anal.* Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.08; H, 3.92. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O non-chelated), 1635 (C=O chelated). The precipitate obtained from the steam-distillation residue was recrystallized from acetone to give bright yellow needles, IV, mp<300°, 25% yield. *Anal.* Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.21; H, 3.86.

b) A stirring mixture of XXIX (4 g), VII (6 g) and conc. H_2SO_4 (100 ml) was heated at 160° for 8 hr. The whole was poured on ice water (300 ml), allowed to stand overnight, and extracted three times with benzene (each 200 ml). The combined benzene extract was concentrated and submitted to thin-layer chromatography (TLC) of silica gel (Wakogel B-5) developing with the solvent system of the upper layer of petroleum ether 5: acetone 5: H_2O 3.5. The fraction of *Rf* 0.98 and 0.71 was extracted with acetone to give XXVIII and IV, which was identical with the foregoing product comparing their IR spectrum and mp, respectively.

c) A mixture of VII (2 g), XXX (8 g), anhyd. $AlCl_3$ (4 g) and $CHCl_2CHCl_2$ (50 ml) was stirred at room temperature for 12 hr. The reaction temperature was raised to 70° and kept for 8 hr. The reaction mixture was poured on ice and dil. HCl, allowed to stand overnight and steam-distilled to remove excess XXX and $CHCl_2CHCl_2$. The resulting residue was shaken with ether. Ether extract was also shaken with 5% Na_2-CO_3 which was acidified with dil. HCl. The resulting precipitate was recrystallized from EtOH to give colorless plates, XXXI, mp 176°, 30.2% yield. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.02; H, 5.43. IR ν_{max}^{KBr} cm^{-1}: 1695 ($-COO^-$), 1657 (C=O). To a stirring molten mixture of anhyd. $AlCl_3$ (10 g) and NaCl (2 g) was added XXXI (1 g) in small portions at 170° and the reaction temperature was maintained for 1 hr. Working up as the foregoing processes of emodin, a) and b) of this run, IV, bright pale yellow needles, mp<300°, 75% yield, was obtained.

d) Compound XXXII[12b] (1 g) was worked up with a molten mixture of anhyd. $AlCl_3$ (10 g) and NaCl (2 g) as the foregoing process of c). As the result, IV was obtained. Yield 60%.

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