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Synthetic Studies on Anthracyclinones. VIII.[1] Synthesis of 4-Bromo-6-ethyl-1-naphthol

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A convenient synthesis of 6-ethyl-1-naphthol(I) and its conversion into 4-bromo-6-ethyl-1-naphthol (VI) are described. Chromium trioxide oxidation of 6-ethyltetralin gave predominantly 6-ethyl-1-tetralone (IX), which was dehydrogenated with palladized charcoal to I. Bromination of I afforded VI, a starting material in the synthesis of bisanhydrodaunomycinone (V). Structuers of VI and IX were confirmed by alternative syntheses as shown in Chart 3.

6-Ethyl-1-naphthol (I) was first synthesized by Ollis, *et al.*[3] from 5-methoxy-2-tetralone in the synthesis of demethoxycarbonyl-η-pyrromycinone, and subsequently employed as a starting material in the synthesis of demethoxycarbonylbisanhydro-ε-rhodomycinone (II) by Brockmann, *et al.*,[4] who condensed I with 3-hydroxyphthalic anhydride and subsequently brominated the condensation product (III) to 4-bromo-1-naphthol derivative (IV) in order to introduce 4-hydroxyl group by replacement of the bromo group in the later step.

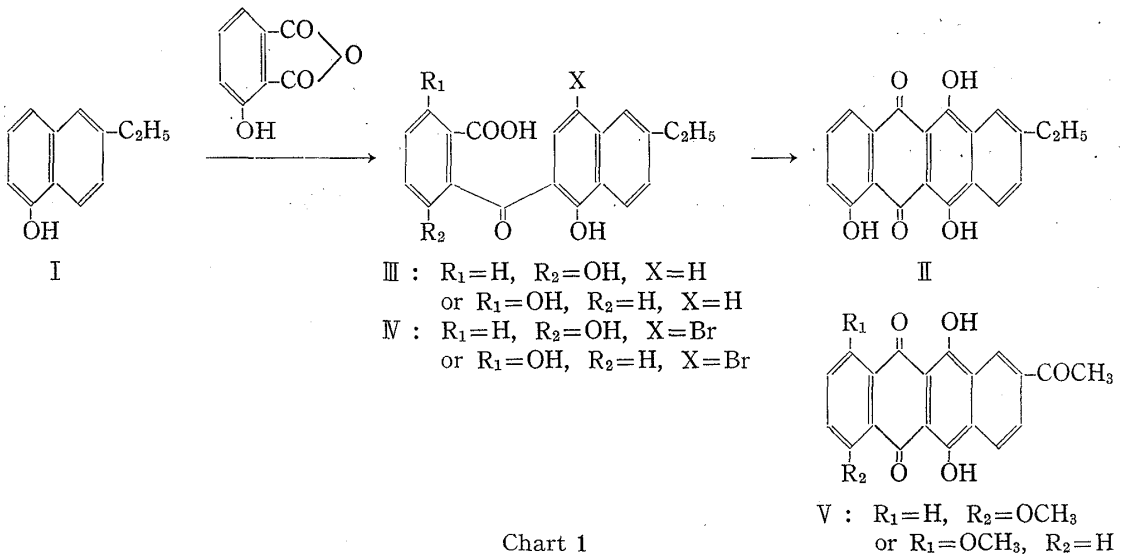

Chart 1

In the studies concerning the synthetic approach to bisanhydrodaunomycinone (V) *via* oxidation of II, the present authors have expected that the Friedel–Crafts condensation of 3-methoxyphthalic anhydride[5] with 4-bromo-6-ethyl-1-naphthol (VI) would provide an efficient and simple route to II. The present paper describes a convenient synthesis of I from

1) Part VII: Z. Horii, H. Hakusui, and T. Momose, *Chem. pharm. Bull.* (Tokyo), **16**, 1262 (1968).
2) Location: *6-5 Toneyama, Toyonaka, Osaka.*
3) W.D. Ollis, I.O. Sutherland, and P. L. Veal, *Proc. Chem. Soc.*, **1960**, 349.
4) H. Brockmann, R. Zunker, and H. Brockmann Jr., *Ann.*, **696**, 145 (1966).
5) For the behaviour of 3-hydroxy- or 3-methoxyphthalic anhydride on Friedel–Crafts condensation, see Part VI of this series.

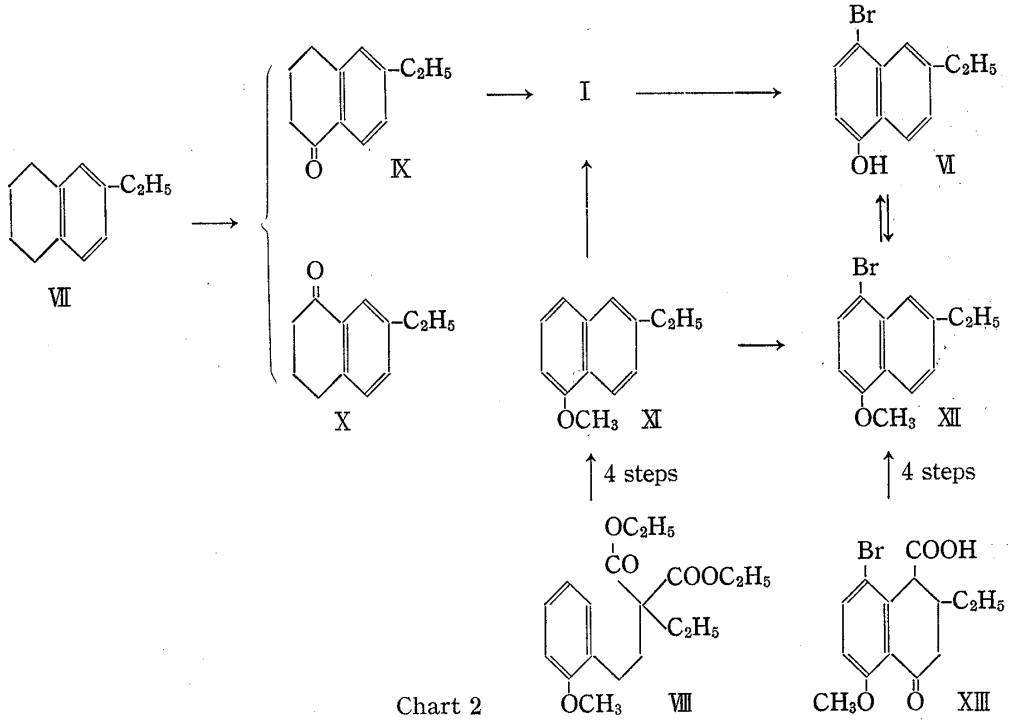

Chart 2

6-ethyltetralin[6] (VII) and subsequent bromination of I to VI. An alternative synthesis of VI from diethyl ethyl [β-(2-methoxyphenyl)ethyl]malonate (VIII) is also described.

Chromium trioxide oxidation of VII in glacial acetic acid gave, in 67% yield, a mixture of 6-ethyl-1-tetralone (IX) and 7-ethyl-1-tetralone[7] (X) in 5:1 ratio, which was determined by gas–liquid chromatography[8] (GLC). Separation of IX from X was effected by using the difference in solubility of their semicarbazones in ethanol. The almost insoluble isomer was treated with pyruvic acid or formalin in acetic acid to give pure IX in 35% or 29% yield from VII. The structures of the isomeric tetralones were confirmed by alternative syntheses which were described below. Dehydrogenation of IX by means of 10% palladized charcoal[9] in boiling cymene gave I, in 69% yield, which was identical with the demethylation product of 2-ethyl-5-methoxynaphthalene[10] (XI). Bromination of I with iodine monobromide[11a] in glacial acetic acid gave VI in 45% yield.

Since the orientation of the bromination was ambiguous as seen in bromination of 2-ethylnaphthalene[12] (mainly 1-bromo-) and α-naphthol[11] (2- and 4-bromo-), the structure of VI was confirmed by the alternative synthesis of its methyl ether (XII) from 8-bromo-2-ethyl-5-methoxy-1,2,3,4-tetrahydro-4-oxo-1-naphthoic acid[10] (XIII) as described below.

6) Preparation of 6-ethyltetralin from 6-acetyltetralin [W. Scharwin, *Ber.*, **35**, 2511 (1902)] has been reported by Fleischer and Siefert [K. Fleischer and F. Siefert, *Ber.*, **53**, 1255 (1902)] without a description of the detailed experimental procedure. The Huang–Minlon reduction by the present authors is suitable for a large scale preparation.

7) 7-Ethyl-1-tetralone has been prepared from 4-(4-ethylphenyl)butyric acid (XVIII) by *a*) Krollpfeiffer and Schäfer [F. Krollpfeiffer and W. Schafer, *Ber.*, **56**, 620 (1923)]; *b*) Lévy [G. Lévy, *Compt. Rend.*, **203**, 337 (1963)]. The melting point of its semicarbazone is greatly different between those reported by both authors. A polyphosphoric acid cyclization of XVIII was also reported by Schenk, *et al.* [G. Schenk, M. Huke, and K. Kuhn, *Tetrahedron Letters*, **1967**, 4711] without a description of the experimental procedure.

8) Analysis was carried out by employing Perkin–Elmer 800 Gas Chromatograph on SE–30.

9) Prepared according to Mozingo's procedure [R. Mozingo, "*Org. Syntheses*," Coll. Vol., **3**, 685 (1955)] with some modifications to prevent from a formation of colloidal palladium. See the experimental part.

10) Z. Horii, T. Momose, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **13**, 651 (1965).

11) *a*) W. Militzer, *J. Am. Chem. Soc.*, **59**, 1368 (1937); *b*) H. Cassebaum, *Chem. Ber.*, **90**, 1537 (1957).

12) R.C. Fuson and D.H. Chadwick, *J. Org. Chem.*, **13**, 484 (1948).

Syntheses of IX, and X and XII by unambiguous procedure

3-Ethylbromobenzene[13] (XIV) was prepared by Huang–Minlon reduction of 3-bromoacetophenone,[13] and was condensed with β-methoxycarbonylpropionyl chloride[14] *via* the cadmium reagent[15] to give methyl 3-(3-ethylbenzoyl)propionate (XV), in 51% yield, which was hydrolysed to the corresponding acid (XVI). The Huang–Minlon reduction of XVI and subsequent cyclization of the resulting butyric acid (XVII) with polyphosphoric acid gave tetralone IX. Tetralone X was prepared by cyclization[7] of 4-(4-ethylphenyl)butyric acid (XVIII) with polyphosphoric acid. Compound XII was prepared from XIII by successive decarboxylation, sodium borohydride reduction, dehydration and dehydrogenation with chloranil, in which the intermediates were the bromo–tetralone (XIX), the bromotetralol (XX) and the dihydronaphthalene (XXI), respectively. Dehydrogenation of XXI with sulfur or palladized charcoal gave only XI from simultaneous debromination.

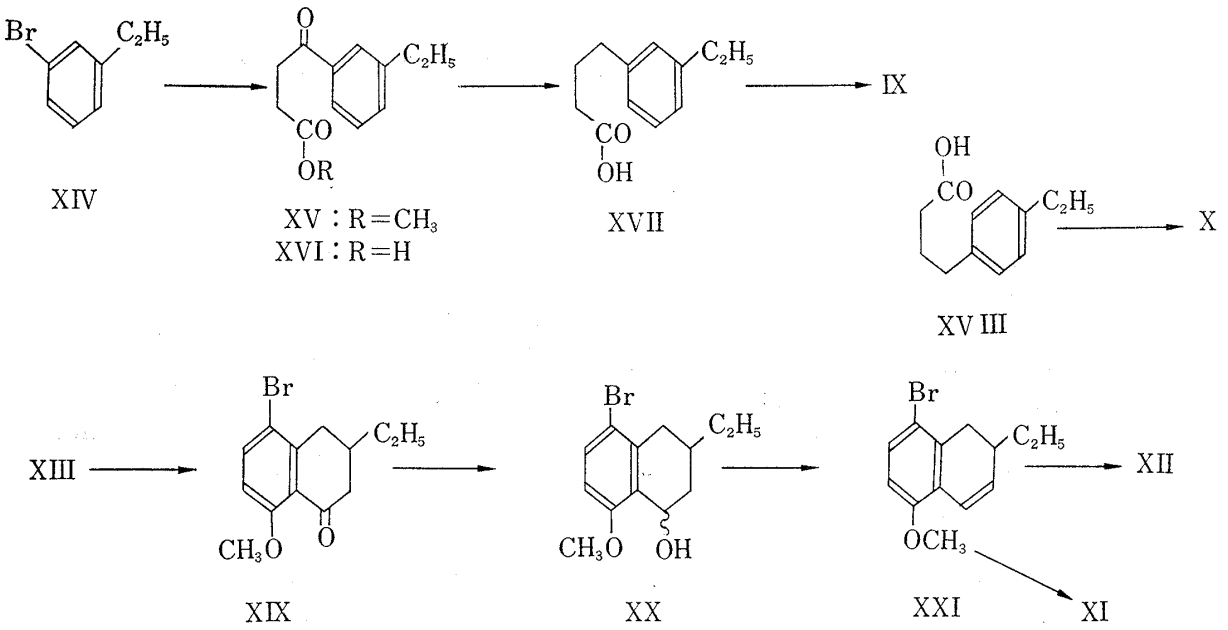

Chart 3

Another approach to XII through 8-bromo-2-ethyl-5-methoxy-1-tetralone (XXII) was unsuccessful because of a failure[16] in cyclization of 2-ethyl-4-(5-bromo-2-methoxyphenyl) butyric acid (XXIII) by polyphosphoric acid or sulfuric acid to XXII, while its debromo derivative (XXIV), prepared from VIII by alkaline hydrolysis and subsequent decarboxylation, was cyclized with polyphosphoric acid to 2-ethyl-5-methoxy-1-tetralone (XXV) in 63% yield. Sodium borohydride reduction of XXV gave a mixture of diastereoisomeric tetralol (XXVI), which gave XI, in 86% yield, on heating with 20% palladized charcoal[9] at 200—210°. Attempted dehydration of XXVI with *p*-toluenesulfonic acid in methanol gave dimethyl ether (XXVII). Bromination of XI with bromine in chloroform gave XII quantitatively, and demethylation of XII with boron tribromide gave VI in 63% yield.

13) Compound XIV has been prepared by the Clemmensen reduction of corresponding acetophenone [G.W. Pope and M.T. Bogert, *J. Org. Chem.*, **2**, 176 (1938)]. The Huang–Minlon procedure is suitable for a short time and large scale preparation.
14) J. Cason, "*Org. Syntheses*," Coll. Vol., **3**, 169 (1955).
15) *cf.* W.G. Dauben and H. Tilles, *J. Org. Chem.*, **15**, 785 (1950).
16) Unsuccessful cyclization to *ortho* position to bromo group in the benzene ring has been encountered previously. *cf.* Z. Horii, T. Momose, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **10**, 946 (1962).

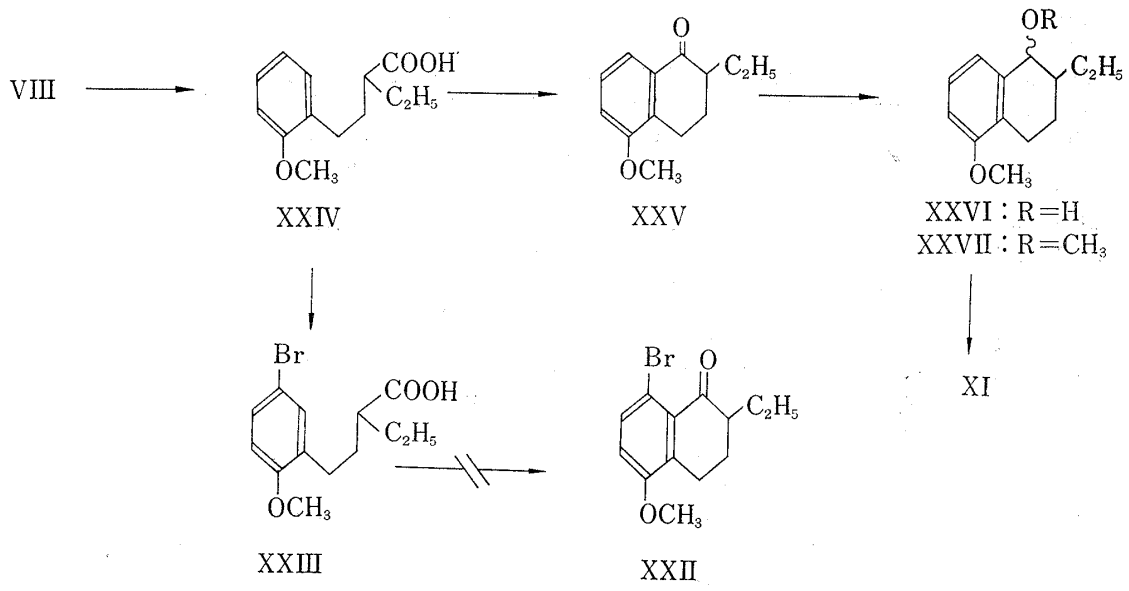

Chart 4

Experimental[17]

6-Ethyl-1,2,3,4-tetrahydronaphthalene (VII)——6-Acetyltetralin[6] was prepared, in 73% yield, from anhyd. $AlCl_3$ (700 g), AcCl (400 g) in ethylene dichloride (500 ml) and tetralin (200 g) in ethylene dichloride (250 ml) under the reaction condition of 15°×30 min and 60°×2 hr. A mixture of 6-acetyltetralin (196 g), KOH (440 g), 80% hydrazine hydrate (360 g) and diethylene glycol (2 liters) was heated at 150° for 1 hr and then at 190° for 3 hr under reflux. The cooled mixture was poured into 2 liters of ice water and extracted with ether. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was fractionated *in vacuo* to give 143 g (80%) of VII as colorless oil, bp 100—105° (6 mmHg).

3-Ethylbromobenzene (XIV)[13]——A mixture of 3-bromoacetophenone[13] (230 g), KOH (220 g), 80% hydrazine hydrate (230 g) and diethylene glycol (1.1 liters) was refluxed at 150° (bath) for 1 hr and then at 190° (bath) for 3 hr. The cooled mixture was poured into 1 liter of ice water, and extracted with ether. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residual oil was fractionated *in vacuo* to give 205 g (96%) of XIV as colorless oil, bp 98° (26 mmHg).

Methyl 3-(3-Ethylbenzoyl)propionate (XV)——A solution of XIV (50 g) in anhyd. ether (150 ml) and anhyd. benzene (50 ml) was added dropwise to Mg turnings (7.8 g) over a period of 1 hr and the mixture was heated under reflux for an additional 1 hr. The Grignard solution was cooled in an ice bath and to this was added anhyd. $CdCl_2$ (35 g) in one portion. The resulting mixture was heated under reflux with stirring for 30 min. The ether was distilled until the mixture became a thin slurry, and to this was added anhyd. benzene (200 ml), 25 ml portion of which was then distilled. A solution of β-methoxycarbonylpropionyl chloride[14] (57.5 g) in anhyd. benzene (50 ml) was added with vigorous stirring to the hot mixture rapidly, and the mixture was heated under reflux with stirring for 2 hr and poured onto a mixture of conc. H_2SO_4 (18 ml) and ice (1 kg). Benzene extraction and fractional distillation gave 30 g (51%) of XV as colorless oil, bp 139° (3 mmHg). *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.08; H, 7.36. IR ν_{max}^{film} cm^{-1}: 1733, 1683 (C=O).

3-(3-Ethylbenzoyl)propionic Acid (XVI)——A mixture of XV (30 g), MeOH (60 ml), KOH (23 g) and H_2O (110 ml) was refluxed for 12 hr, and then MeOH was removed by evaporation. The cooled mixture was shaken twice with ether, and the aqueous layer was acidified with 10% HCl and extracted with ether. The extract was washed with satd. aq. NaCl, dried over anhyd. Na_2SO_4 and evaporated to give 20 g (72%) of XVI as a pale yellow solid, mp 64—71°. Recrystallization from H_2O gave an analytical sample as colorless needles, mp 74°. *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.16; H, 6.66. IR ν_{max}^{KBr} cm^{-1}: 1677 (C=O); $\nu_{max}^{CCl_4}$ cm^{-1}: 1705, 1686 (C=O).

4-(3-Ethylphenyl)butyric Acid (XVII)——A mixture of XVI (18 g), KOH (20.7 g), 80% hydrazine hydrate (16.4 g) and diethylene glycol (100 ml) was refluxed at 150° (bath) for 1 hr and at 190° (bath) for 3 hr. The cooled mixture was poured into ice water, acidified with dil. HCl and extracted with ether. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was fractionated *in vacuo*

17) All melting points and boiling points are uncorrected. NMR spectra were taken on Hitachi H-6013 spectrometer with Me_4Si as the internal standard.

to give 10.5 g (63%) of XVII as colorless oil, bp 141° (3 mmHg). *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.04; H, 8.39. IR ν_{max}^{film} cm^{-1}: 1705 (C=O).

6-Ethyl-3,4-dihydro-1(2*H*)-naphthalenone (IX)——A mixture of XVII (7.2 g) and polyphosphoric acid (144 g) was heated with stirring at 80° until the color of the mixture became dark brown (1 hr) and poured into ice water. The oily material was extracted with ether, and the extract was washed with H_2O, satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was fractionated *in vacuo* to give 5.0 g (77%) of IX as colorless oil, bp 153° (8 mmHg). Only trace of 8-ethyltetralone was detected in the product by GLC analysis. *Anal.* Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.51; H, 8.18. IR ν_{max}^{film} cm^{-1}: 1678 (C=O). Semicarbazone: pale yellow crystals from EtOH, mp 212°. *Anal.* Calcd. for $C_{13}H_{17}ON_3$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.46; H, 7.26; N, 18.23. IR ν_{max}^{KBr} cm^{-1}: 3425, 3205, 1681, 1618, 1580. Oxime: colorless plates, mp 94—96°, bp 170—175° (2 mmHg). *Anal.* Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.33; H, 7.92; N, 7.27. IR ν_{max}^{KBr} cm^{-1}: 3215.

7-Ethyl-3,4-dihydro-1(2*H*)-naphthalenone (X)——4-(4-Ethylphenyl)butyricacid (XVIII)[7] was prepared, in 69% yield, by Huang-Minlon reduction of 3-(4-ethylbenzoyl)propionic acid.[7a] A mixture of XVIII (10 g) and polyphosphoric acid (200 g) was heated at 80° for 20 min, then poured into ice water, and extracted with benzene. The extract was washed with H_2O, satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was fractionated *in vacuo* to give 7.8 g (86%) of X as colorless oil, bp 148—149° (5 mmHg). Semicarbazone: pale yellow crystals from EtOH, mp 190° (lit.,[7a] mp 223—225°; lit.,[7b] mp 197°). *Anal.* Calcd. for $C_{13}H_{17}ON_3$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.28; H, 7.41; N, 18.34. IR ν_{max}^{KBr} cm^{-1}: 3413, 3205, 1681, 1580. Oxime: Colorless crystals, mp 45—47°, bp 170° (2 mmHg). *Anal.* Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99. Found: C, 76.01; H, 7.93. IR ν_{max}^{KBr} cm^{-1}: 3247.

Oxidation of VII——To a cooled solution of VII (143 g) in AcOH (800 ml) was added dropwise a solution of CrO_3 (143 g) and H_2O (72 ml) in AcOH (400 ml) with stirring over 1.5 hr, and the mixture was allowed to stand overnight at room temperature, poured into ice water, acidified to congo red with conc. HCl and extracted with benzene. The extract was washed with H_2O, satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 140 g of a pale yellow oil, which was subjected to fractional distillation. Forty-five grams of VII was recovered, and a fraction of bp 135—145° (6 mmHg) (80 g) was redistilled to give 69 g (67% on subtraction of recovered VII) of a mixture of tetralones as almost colorless oil, bp 128—130° (2 mmHg), which showed two peaks with areas of 1:5 in the sequence of increasing retention time on GLC analysis.

Semicarbazone of the Tetralone Mixture——To a solution of the tetralone mixture (5 g) in EtOH (50 ml) was added semicarbazide hydrochloride (8 g), $AcONa \cdot 3H_2O$ (11.8 g) and H_2O (30 ml), and the mixture was heated at 80° with stirring for 15 min. Pale yellow precipitates deposited immediately. The cooled mixture was filtered to give 6 g of the semicarbazone, which was recrystallized twice from EtOH to give 3.9 g of pure semicarbazone of IX as pale yellow crystals, mp 208—212°, which was identified, by IR (KBr) comparison, with the authentic sample prepared above. From the mother liquor of the recrystallization was obtained 0.7 g of semicarbazone of X as pale yellow crystals, mp 190°, which was identified with the authentic sample prepared above by IR (KBr) comparison.

Regeneration of IX from Its Semicarbazone——*a*) By pyruvic acid: To a solution of the semicarbazone (3.9 g) in AcOH (30 ml) was added a mixture of pyruvic acid (15.4 g) in H_2O (5 ml). The mixture was refluxed for 20 min, then poured into 150 ml of H_2O, and extracted with $CHCl_3$. The extract was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residual oil was fractionated *in vacuo* to give 2.73 g (89%) of IX as colorless oil, bp 135—138° (6 mmHg), which was identified, by IR (in CCl_4) comparison and by GLC, with the authentic sample prepared above.

b) By formalin: To a solution of the semicarbazone (65 g) in AcOH (330 ml) was added 37% formalin (145 ml), and the mixture was refluxed for 30 min, then poured into ice water, acidified with 10% HCl to congo red, and extracted with benzene. The extract was washed with H_2O, satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was fractionated *in vacuo* to give 36.3 g (74%) of IX as colorless oil, bp 115—119° (2 mmHg).

Palladium on Carbon Catalyst (10% Pd)——A solution of palladium chloride (2 g) in conc. HCl (10 ml) was diluted with H_2O (24 ml), and to this was added activated charcoal[18] (10 g) with stirring. After 10 min's stirring, the suspension was diluted with H_2O (120 ml) and heated at 80° for 15 min, followed by addition of 37% formalin (6 ml). The stirred suspension was made slightly alkaline to lithmus with 30% aq. NaOH, followed by 5 min's heating at 80°. The mixture was allowed to cool with stirring, and filtered. The catalyst was washed with H_2O until the washings became neutral to lithmus, and dried on a steam bath for 2 hr.

The catalyst of 20% Pd was prepared analogously by using 5 g of charcoal.

6-Ethyl-1-naphthol (I)——A mixture of IX (30 g), 10% palladized charcoal (21 g) and cymene (150 ml) was refluxed for 7 hr, cooled and filtered. The residual catalyst was washed thrice with ether, and the filtrate and the washings were combined and extracted with 7% NaOH until no more naphthol was extracted.

18) Commercial active charcoal "Tokusei-Shirasagi "from Takeda Pharmaceutical Co., Ltd. was used after 2 hr's drying at 100° without acid washing.

The alkaline layer was shaken with ether, filtered, acidified with 10% HCl and extracted with ether (100 ml × 3). The extract was washed with satd. $NaHCO_3$ and satd. NaCl, dried over anhyd. Na_2SO_4 and evaporated. Fractional distillation of the residue gave 15 g (69% on subtraction of recovered IX) of I as colorless crystals, mp 60—65°, bp 140—145° (3 mmHg), which was identified with the authentic sample[10] by IR (KBr) comparison. From the neutral layer after extraction with alkali was recovered 8 g of IX.

4-Bromo-6-ethyl-1-naphthol (VI)——To a solution of bromine (2.1 g) in AcOH (15 ml) was added iodine (3.5 g), and the mixture was warmed at 50° with stirring. The resulting iodine monobromide solution was added to a solution of I (2.25 g) in AcOH (25 ml) within 10 min with stirring under N_2 at ice-cooling condition, and the mixture was stirred at room temperature for 2 hr, poured into H_2O (200 ml) containing Na_2SO_3 and extracted with ether (30 ml × 4). The extract was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was crystallized from 33% EtOH to give 1.5 g (45%) of VI as slightly brownish crystals, mp 100—110°. Three recrystallizations from 33% EtOH afforded an analytical sample as colorless crystals, mp 114—116°. *Anal.* Calcd. for $C_{12}H_{11}OBr$: C, 57.39; H, 4.42. Found: C, 57.10; H, 4.32. IR ν_{max}^{KBr} cm^{-1}: 3257 (OH), 1621, 1603, 1567 (arom.).

5-Bromo-3-ethyl-8-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (XIX)——To a solution of 8-bromo-2-ethyl-5-methoxy-1,2,3,4-tetrahydro-4-oxo-1-naphthoic acid[10] (XIII) (10 g) in quinoline (10 ml) was added freshly prepared copper powder,[19] and the mixture was heated at 200° for 1.5 hr, cooled, poured into 10% H_2SO_4 (50 ml) and extracted with $CHCl_3$ (25 ml × 3). The extract was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 8.7 g of a colorless oil. Fractional distillation gave 8.5 g (97%) of XIX as colorless oil, bp 173—174° (4 mmHg). *Anal.* Calcd. for $C_{13}H_{15}O_2Br$: C, 55.12; H, 5.33. Found: C, 55.27; H, 5.20. IR ν_{max}^{film} cm^{-1}: 1686 (C=O).

5-Bromo-3-ethyl-1-hydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene (XX)——To a stirred and ice-cooled solution of $NaBH_4$ (1.9 g) in MeOH (35 ml) was added a solution of XIX (7 g) in MeOH–ether (1:1, 40 ml), and the mixture was stirred under ice-cooling for 2 hr and at room temperature for an additional 1.5 hr, poured into cold satd. NaCl (80 ml) and extracted with ether (40 ml × 3). The extract was washed with satd. NaCl, dried over anhyd. Na_2SO_4 and evaporated to give 6.5 g of a viscous oil, which was purified by column chromatography on silica gel–$CHCl_3$ system to give 6.3 g (92%) of XX as colorless oil. *Anal.* Calcd. for $C_{13}H_{17}O_2Br$: C, 54.74; H, 6.25. Found: C, 55.09; H, 5.90. IR ν_{max}^{film} cm^{-1}: 3571 (OH).

8-Bromo-2-ethyl-5-methoxy-1,2-dihydronaphthalene (XXI)——A solution of XX (4 g) and $POCl_3$ (3.5 g) in dry benzene (30 ml) was refluxed for 50 min and poured into ice water (50 ml). The benzene layer was separated, and the aqueous layer was extracted with benzene (30 ml × 2). The combined benzene layer was washed with H_2O, satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 2.8 g of a colorless oil. Purification by column chromatography on silica gel–$CHCl_3$ system gave 2.5 g (67%) of XXI as colorless oil, bp 120° (0.01 mmHg). *Anal.* Calcd. for $C_{13}H_{15}OBr$: C, 58.36; H, 5.36. Found: C, 59.17; H, 5.58. IR $\nu_{CCl_4}^{max}$ cm^{-1}: 1626 (C=O). NMR (10% solution in CCl_4) τ: 4.17 (1H, doublet of doublets, J=12 cps, 4 cps, C_3-H), 3.33 (1H, doublet of doublets, J=12 cps, 2 cps, C_4-H), 3.52 (1H, doublet, J=10 cps, C_6-H), 2.81 (1H, doublet, J=10 cps, C_7-H).

Diethyl Ethyl[β-(2-methoxyphenyl)ethyl]malonate (VIII)——To a suspension of NaH (50% in oil, 9.8 g) in dry benzene (200 ml) was added diethyl β-(2-methoxyphenyl)ethylmalonate[20] (40 g) with stirring over 30 min, and the mixture was stirred on a steam bath for an additional 30 min. To this was added a solution of ethyl iodide (42 g) in dry benzene (20 ml) with stirring over 30 min, and the mixture was refluxed with stirring for 5 hr. Water (200 ml) was added to the cooled mixture, and the benzene layer was separated. The aqueous layer was extracted with benzene (50 ml × 3), and the combined benzene layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Fractional distillation of the residue gave 41.1 g (94%) of VIII as colorless oil, bp 167—173° (4 mmHg), which solidified on standing. Three recrystallizations from *n*-hexane afforded an analytical sample as colorless plates, mp 55—56°. *Anal.* Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.21; H, 7.95. IR ν_{max}^{KBr} cm^{-1}: 1724 (C=O).

2-Ethyl-4-(2-methoxyphenyl)butyric Acid (XXIV)——A mixture of KOH (25 g), VIII (40 g) and 50% aq. EtOH (100 ml) was refluxed for 1.5 hr. After evaporation of EtOH, H_2O (100 ml) was added to the mixture, follow by shaking with ether (30 ml × 2). The aqueous layer was acidified with 10% HCl and ice and extracted with ether (50 ml × 3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 32 g of crystals, which was heated at 200—205° for 10 min and then distilled at 180° (bath). A colorless oil, bp 169—172° (4 mmHg), was obtained. Yield: 24 g (87%). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.14; H, 8.04. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1698 (C=O).

2-Ethyl-4-(5-bromo-2-methoxyphenyl)butyric Acid (XXIII)——To a solution of XXIV (24 g) in $CHCl_3$ (200 ml) was added a solution of Br_2 (18 g) in $CHCl_3$ (100 ml) under ice-cooling over 5 hr, and the mixture was stirred at room temperature for an additional 30 min, washed with H_2O (50 ml × 2), 10% $Na_2S_2O_3$ and H_2O (50 ml × 3), dried over anhyd. Na_2SO_4 and evaporated. Fractional distillation of the residue gave 32 g of XXIII as colorless oil, bp 160—165° (0.01 mmHg), which solidified on standing. mp 50—58°. *Anal.*

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Calcd. for $C_{13}H_{17}O_3Br$: C, 51.84; H, 5.69; Br, 26.53. Found: C, 51.93; H, 5.65; Br, 26.08. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1703 (C=O).

2-Ethyl-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (XXV)——A mixture of XXIV (13 g) and polyphosphoric acid (300 g) was heated at 100° for 12 min, poured onto cracked ice (300 g) and extracted with ether (50 ml×3). The extract was washed with H_2O, twice with satd. $NaHCO_3$ and twice with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 11 g of an oil. Fractional distillation gave 7.5 g (63%) of XXV as colorless oil, bp 119—120° (2 mmHg). *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.35; H, 7.87. IR ν_{max}^{film} cm^{-1}: 1682 (C=O).

2-Ethyl-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (XXVI)——To an ice cooled solution of $NaBH_4$ (1.8 g) in MeOH (20 ml) was added with stirring a solution of XXV (7 g) in ether (10 ml) over 20 min, and the mixture was stirred at room temperature for 1 hr, poured into satd. NaCl (100 ml) and extracted with ether (50 ml×2). The extract was washed with satd. NaCl, dried over anhyd. Na_2SO_4 and evaporated to give 7.1 g of a colorless viscous oil, which solidified on standing. Recrystllization from *n*-hexane (50 ml) gave 6.9 g (98%) of XXVI as colorless fibers, mp 91—93°. *Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.57; H, 8.81. IR ν_{max}^{KBr} cm^{-1}: 3379 (OH).

2-Ethyl-1,5-dimethoxy-1,2,3,4-tetrahydronaphthalene (XXVII)——A solution of XXVI (6 g) and TsOH (0.2 g) in MeOH (40 ml) was refluxed for 2 hr. After evaporation of MeOH, the mixture was diluted with benzene (50 ml), washed with H_2O, satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 6.2 g of a colorless oil. Fractional distillation gave 5.6 g (88%) of XXVII as colorless oil, bp 123-125° (3 mmHg). *Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.37; H, 8.95.

2-Ethyl-5-methoxynaphthalene (XI)——A mixture of XXVI (5 g) and 20% palladized charcoal (0.5 g) was heated at 170—200° for 10 min, 200—210° for 2 hr, and 210—230° for 30 min. The mixture was diluted with ether (20 ml) and filtered. The filtrate was evaporated and distilled *in vacuo* to give 3.7 g (82%) of XI as colorless oil, bp 130—135° (2 mmHg), which was identified with the authentic sample[10] by IR (film) comparison.

4-Bromo-6-ethyl-1-methoxynaphthalene (XII)——*a*) From VI: A mixture of VI (0.3 g), anhyd. K_2CO_3 (4 g), MeI (4 ml) and acetone (10 ml) was refluxed for 9 hr. After removal of the solvent, the residual mass was extracted with hot $CHCl_3$ (10 ml×3), and the $CHCl_3$ layer was evaporated. Purification of the residue by column chromatography on silica gel–benzene system followed by fractional distillation gave 110 mg (35%) of XII as colorless oil, bp 140—145° (2 mmHg). *Anal.* Calcd. for $C_{13}H_{13}OBr$: C, 58.88; H, 4.94; Br, 30.15. Found: C, 58.62; H, 4.93; Br, 29.70. NMR (CCl_4) τ: 1.93 (1H, doublet, J=8 cps, C-8-H), 2.14 (1H, broad singlet, C-5-H), 2.51 (1H, doublet, J=8 cps, C-3-H), 2.73 (1H, doublet of doublets, J=8 cps, $J_{5,7}$=1.7 cps, C-7-H), 3.54 (1H, doublet, J=8 cps, C-2-H), 6.12 (3H, singlet, OCH_3), 7.16 (2H, quartet, J=7 cps, $\underline{CH_2}$-CH_3), 8.65 (3H, triplet, J=7 cps, CH_2-$\underline{CH_3}$).

b) From XI: To an ice-cooled and stirred mixture of XI (9.3 g), anhyd. NaOAc (8.2 g) and $CHCl_3$ (100 ml) was added a solution of Br_2 (8.8 g) in $CHCl_3$ (50 ml) over 2 hr, and the mixture was stirred for an additional 1 hr and poured into ice-water (100 ml). The $CHCl_3$ layer was washed with H_2O, satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated. Fractional distillation of the residue gave 11.8 g (89%) of XII as colorless oil, bp 140—145° (2 mmHg), which was identified with the sample prepared in *a*) by IR (film) comparison.

c) From XXI: A mixture of XXI (1 g), chloranil (0.93 g) and xylene (10 ml) was refluxed for 6 hr under N_2, cooled and diluted with petroleum ether (50 ml). The precipitates of the quinol and unchanged quinone was separated and washed with hot petroleum ether. The combined petroleum ether layer was evaporated to give 0.83 g (84%) of XII as colorless oil, which was identified with the sample prepared in *a*).

Demethylation of XII with BBr_3——To a solution of XII (0.5 g) in dry CH_2Cl_2 (10 ml) was added at −60° a solution of BBr_3 (4.73 g) in dry CH_2Cl_2 (7 ml), and the mixture was allowed to stand for 2 hr at room temperature, poured onto cracked ice (40 g) and extracted with ether (20 ml×3). The extract was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 0.39 g of brownish solid. Recrystallization from CCl_4 gave 0.3 g (63%) of VI as colorless needles, mp 114—116°, which was identified with the authentic sample by IR (KBr) comparison.