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Synthetic Studies on Anthracyclinones. IX.[1] Lithiation of N,N-Dimethylnaphthalenemethylamines and a New Synthetic Pathway to 2,3-Naphthalides

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Lithiation of ring-methoxylated N,N-dimethylnaphthalenemethylamines was investigated. The lithiation of 4-methoxy-2-naphthalenemethylamine types (XV and XVII) resulted in a selective lithiation on position 3, leading to an efficient method of β, β'-bis-carbon-substitution on the naphthalene or anthracene ring system. As an application, new syntheses of 1-oxygenated 2,3-naphthalides (XXXII, XXXIII, XXXV, and XXXVI) or 5-oxygenated 2,3-naphthalides (XLII) were accomplished *via* carboxylation of lithio derivatives, quarternarization of the resulting amino acids and subsequent pyrolysis.

In the preliminary experiment for construction of the aliphatic A-ring of anthracyclinones (I), it was needed for the present authors to introduce two carbon-chains on the position 2 and 3 of anthracene system (II) which might be cyclized to form the 1,2,3,4-tetrahydronaphthacene ring system (III). As the exploratory experiment, the stepwise introduction of bis-carbon-substituents on C_2 and C_3 of the naphthalene ring by lithiation was investigated.

Lithiation of N,N-Dimethylnaphthalenemethylamines

The naphthalene ring bearing carbon-chain on C_2 is considerably difficult to introduce the second carbon-chain on C_3 as seen in acylation[3] of β-methylnaphthalene or in bromination[4] of β-ethylnaphthalene, in which the position 6 is acylated or the α-position is brominated. Hauser, *et al.*[5] reported a selective *ortho* lithiation of benzyldimethylamine (IV) in 1963 and its application to α- and β-N,N-dimethylnaphthalenemethylamine (V and VI) in 1967. In order to examine the applicability of this lithiation to the selective $C_{2,3}$-dialkylation of the naphthalene system, the present authors have checked the lithiation of V and VI by carboxylation of the lithio-derivative with carbon dioxide and investigated the lithiation pattern in the ring-methoxylated N,N-dimethylnaphthalenemethylamines.

Benzyldimethylamine (IV) was lithiated with butyl lithium and treated with carbon dioxide. The amino acid produced was extracted using anion exchange resin and characterized as the methyl ester (VII) by treatment of its hydrochloride with diazomethane. Yield was 35% from IV. Similar treatment of V gave N-methylnaphthalimide (VIII) in 57% yield, but β-carboxylated product, methyl 1-dimethylaminomethyl-2-naphthoate (IX) failed to be isolated. In the detailed experiment, it was found that major part of the evaporated amino acid fraction, eluted from anion exchange resin with hydrochloric acid, could be extracted with chloroform prior to esterification. The extracted material was shown, from infrared (IR) spectrum and thin-layer chromatography (TLC) analysis, to be N-Methyl-

1) Part VIII: Z. Horii, S. Yamamura, H. Hakusui, T. Nishikado, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **16**, 2456 (1968).
2) Location: *6-5 Toneyama, Toyonaka, Osaka.*
3) R.D. Haworth, B.M. Letsky, and C.R. Mavin, *J. Chem. Soc.*, **1932**, 1784.
4) R.C. Fuson and D.H. Chadwick, *J. Org. Chem.*, **13**, 484 (1948).
5) *a*) F.N. Jones, R.L. Vaulx, and C.R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963); *b*) R.L. Gay and C.R. Hauser, *J. Am. Chem. Soc.*, **89**, 2297 (1967).

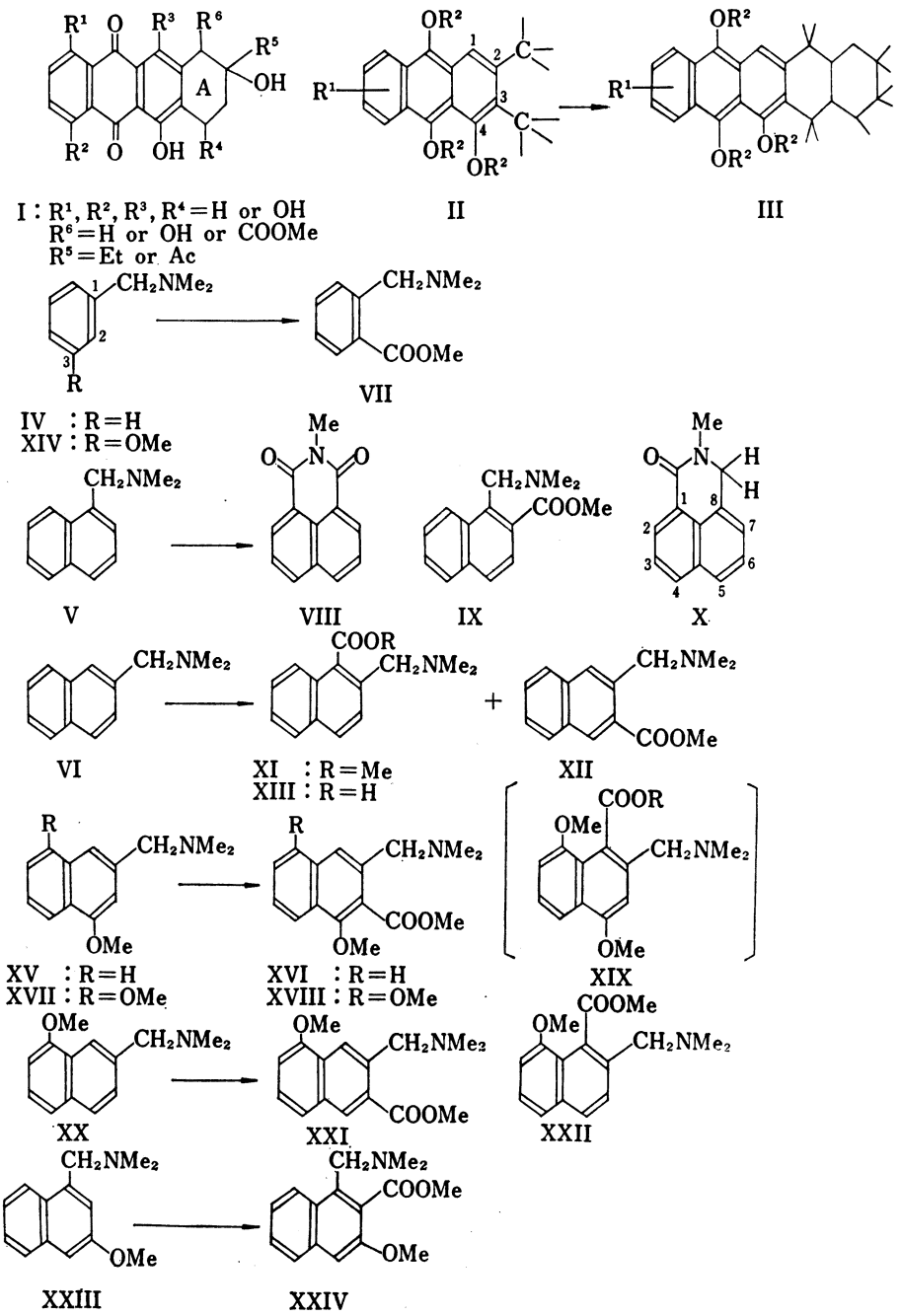


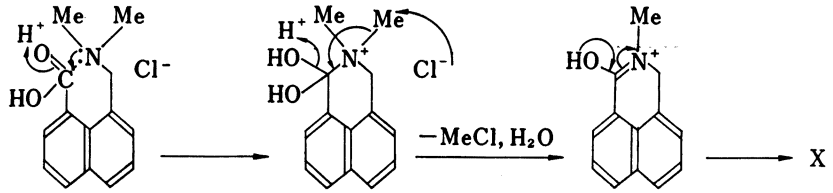
Chart 1

naphthalimidine[6] (X) accompanied with a trace of the imide (VIII). The lactam (X) showed molecular ion peak[7] at *m/e* 197 with the second intensity and $(M-H)^+$ ion peak[7] at *m/e* 196

6) The lactam (X) have been prepared, by Sakurai, from IX by electrolytic reduction, and shown to be basic enough to form the hydrochloride [B. Sakurai, *Bull. Chem. Soc. Japan*, **14**, 173 (1939)].

7) These fragment ions are absent in MS of the imide (IX), in which the molecular ion (211) appears as a base peak.

as a base peak with a metastable ion peak at *m/e* 195 in mass spectrum (MS), IR band at 1645 cm^{-1} due to lactam carbonyl, and NMR signals of two-proton singlet at 5.13 τ due to lactam methylene (CO-N-CH_2-Ar) and of three-proton singlet at 6.81 τ due to N-methyl, and was found to be rapidly oxidized in the air to the imide (VIII). Accordingly, it is evident that cyclization of the 1,8-amino-acid have occurred in the desorption step from anion exchange resin to form the lactam (X), followed by oxidation to VIII during the subsequent working-up. The lactam (X) was presumed to be formed *via* protonation of the carboxyl rather than amino group of the amino acid (a) due to extreme proximity of the carbonyl and aminonitrogen as illustrated in Chart 2.



a

Chart 2

β-Dimethylaminomethylnaphthalene (VI) gave, on similar treatment, an α-naphthoate (XI) and a β-naphthoate (XII) in 29% and 23% yields, respectively. Separation of both isomers was achieved by means of preparative gas-liquid chromatography (GLC) or differential esterification of the amino acid mixture by Fischer's procedure. The hindered amino acid (XIII) was recovered unesterified and could be methylated with diazomethane.

Hauser, *et al.*[5b] estimate the isomer ratio as 91:9 for 8- to 2-lithiation in the α-amine or as 45:55 for 1- to 3-lithiation in the β-amine from nuclear magnetic resonance (NMR) signal of the mixture of benzhydrol derivatives which were obtained by condensation of the lithiated naphthalenes with benzophenone. The lithiating agent containing lithium bromide[8] and the less bulky electrophile such as carbon dioxide employed in the present experiment would have given the inverse isomer ratio in the case of the β-amine (VI).

Hauser, *et al.*[9] have also reported a selective 2-lithiation of 3-methoxybenzyldimethylamine (XIV). Similar results were obtained in the naphthalene system as described below. N,N-Dimethyl-4-methoxy-2-naphthalenemethylamine (XV) gave a 1-methoxy-2-naphthoate (XVI), in 56% yield, as a sole product resulting from the specific lithiation. Although a peri-methoxyl group is also expected to participate in C_1-lithiation of β-dimethylaminomethylnaphthalene from the spatial requirement,[10] N,N-dimethyl-4,8-dimethoxy-2-naphthalenemethylamine (XVII) also gave a single naphthoate (XVIII) in 52% yield, demonstrating that the 8-methoxyl group exerted no influence on C_1-position to yield a 1-naphthoate (XIX) and that these methoxyl participation might be of electronic requrement and not of spatial one. This was confirmed by lithiation of N-N,dimethyl-8-methoxy-2-naphthalenemethylamine (XX), which resulted in a specific C_3-lithiation to yield a 2-naphthoate (XXI) in 38% yield, while an expected 1-naphthoate (XXII) failed to be isolated due to its negligible yield. Rather steric interference would operate in this 2,8-system.

8) Hauser, *et al.* used a commercially available butyllithium free from lithium bromide: see ref. 5*b*.
9) K.P. Klein and C.R. Hauser, *J. Org. Chem.*, **32**, 1479 (1967).
10) Lithiation of 1-methoxynaphthalene has been reported to metallate in C_2- and C_8-position [*a*) R.A. Barnes and L.J. Nehmsmann, *J. Org. Chem.*, **27**, 1939 (1962); *b*) B.M. Graybill and D.A. Shirley, *ibid.*, **31**, 1221 (1966)].

1,3-Methoxyl participation operate even in 1-naphthalenemethylamine system as demonstrated in the lithiation of N,N-dimethyl-3-methoxy-1-naphthalenemethylamine (XXIII), in which only a 2-naphthoate (XXIV) was produced, in 39% yield, without any *peri*-lithiation.

Syntheses of 2,3-Naphthalides

Structures of these naphthoates or position of the specific carboxylations were verified unambiguously by their transformations into naphthalides as described below. In order to ascertain their *ortho*-carboxylation, the anino-esters were quarternarized with methyl iodide, and the resulting methiodides were pyrolyzed at 200—210° to yield γ-lactones.

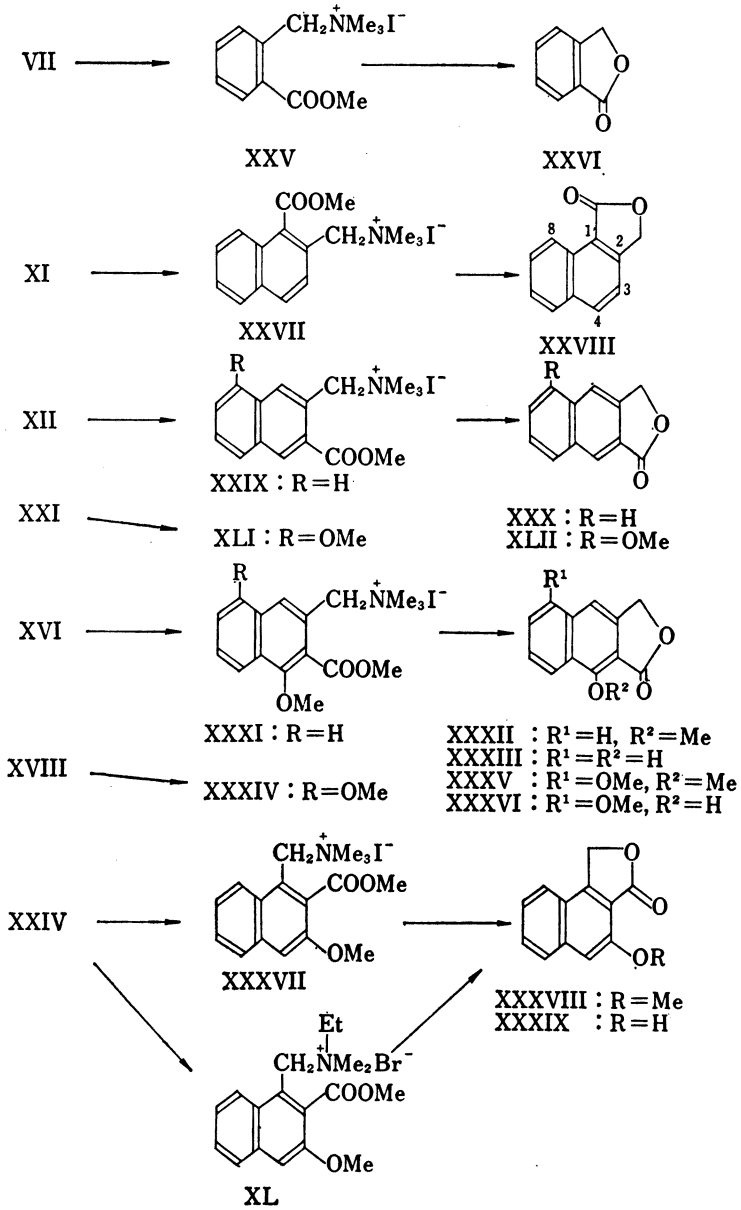


Chart 3

The benzoate (VII) was converted, in 44% yield, into phthalide (XXVI) *via* its methiodide (XXV) by this procedure. The 1,2-[11] and 2,3-naphthalide[12] (XXVIII and XXX) were obtained in 79% and 76% yields from the methiodides XXVII and XXIX, respectively. The structures of XXVIII and XXX were determined from their elemental analyses together with IR- and NMR-measurements. Lactone bands in their IR spectra appear at 1736 cm^{-1} for XXVIII and at 1748 cm^{-1} for XXX. The NMR signal of C_8-proton in XXVIII appears at 1.07 τ as a multiplet, while that of C_1-proton in XXX at 1.44 τ as a singlet.

The cyclization would proceed by concerted elimination of quarternary nitrogen followed by simultaneous S_N2 type attack of highly nucleophilic iodide anion on the methoxyl-methyl[13] as illustrated in Chart 4.

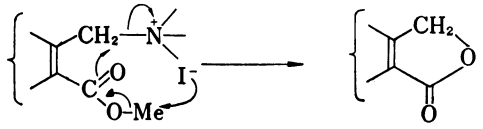


Chart 4

Analogous lactonization of methoxy-amino-ester methiodides XXXI, XXXIV and XXXVII gave methoxynaphthalides XXXIII,[14] XXXV and XXXVIII, in respective yields of 19%, 21% and 15%, accompanied with the corresponding demethylated lactones XXXIII[14,15] (7%) XXXVI (9%) and XXXIX (6%). The structures of XXXIII, XXXVI and XXXIX were assinged from their bathochromically shifted lactone bands and bonded hydroxyl bands in IR spectra (1724 and 3378 cm^{-1}, 1715 and 3390 cm^{-1}, and 1730 and 3410 cm^{-1}, respectively) and from their positive ferric chloride tests. The methoxy-lactone and its demethylate were easily correlated as seen in conversion of XXXIII ito XXXII by methylation or in demethylation of XXXVIII with hydrochloric acid to XXXIX. The demethylation would occur in the ammonium–elimination step by alternative attack of iodide ion on the ether–methoxyl group and not in the secondary stage after cyclization, since the methoxy-lactone (XXXV) was recovered unchanged on heating with tetramethylammonium iodide under the same condition as in the pyrolytic lactonization.

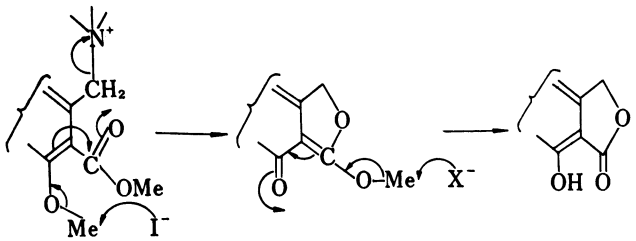


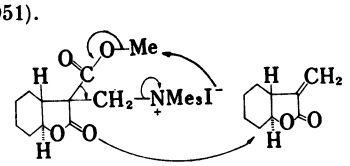
Chart 5

That use of less nucleophilic bromide ion led to an improvement of the yield (26%) of methoxy-lactone and depression of that (4%) of the demethylated product as seen in the pyro-

11) *a*) F. Weygand, K.G. Kinkel, and D. Tietjen, *Chem. Ber.*, **83**, 394 (1950); *b*) F. Mayer, W. Schäfer, and J. Rosenbach, *Arch. Pharm.*, **1929**, 575.

12) K. Yagi, *Mem. Inst. Sci. Ind. Research, Osaka Univ.*, **8**, 200 (1951).

13) Related ammonium-iodide-participation in ester cleavage has been reported [E.S. Behare and R.B. Miller, *Chem. Commun.*, **1970**, 402]. A concerted mechanism shown below would be reasonable.



14) Z. Horii, T. Katagi, Y. Tamura, and T. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **10**, 887 (1962).

15) Z. Horii, T. Katagi, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **11**, 317 (1963).

lysis of the ethobromide (XL), and that no methoxyl cleavage was recognized in conversion of the 5-methoxy-2-naphthoate methiodide (XLI) into the naphthalide (XLII) (44%) by these treatment may support the above proposal.

Somewhat lower yields of the methoxy-lactones would be attributed to the non-coplanarity, in the elimination step, of the ester carbonyl with aromatic ring due to steric hindrance from both *ortho* substitution. The ester-carbonyl bands of extraordinarily high frequency (1733 cm^{-1} for XVIII and XXIV) in IR spectra are in good agreement with their considerable steric hindrance.

The syntheses of these 1-oxygenated 2,3-naphthalides would provide a new synthetic route to 7-oxygenated phthalides or 1-oxygenated 2,3-naphthalides such as α- and β-sorigenin whose syntheses[16] have been laborious so far.

Syntheses of Ring-Methoxylated N,N-Dimethylnaphthalenemethylamines

The amine (XV) was synthesized from ethyl hydrogen benzylidenesuccinate[17] by 5-step procedure *via* an acetoxynaphthoate (XLIII), a hydroxynaphthoic acid[18] (XLIV), a methoxynaphthoate (XLV), and a naphthalenemethanol (XLVI). A mixture of *cis*- and *trans*-

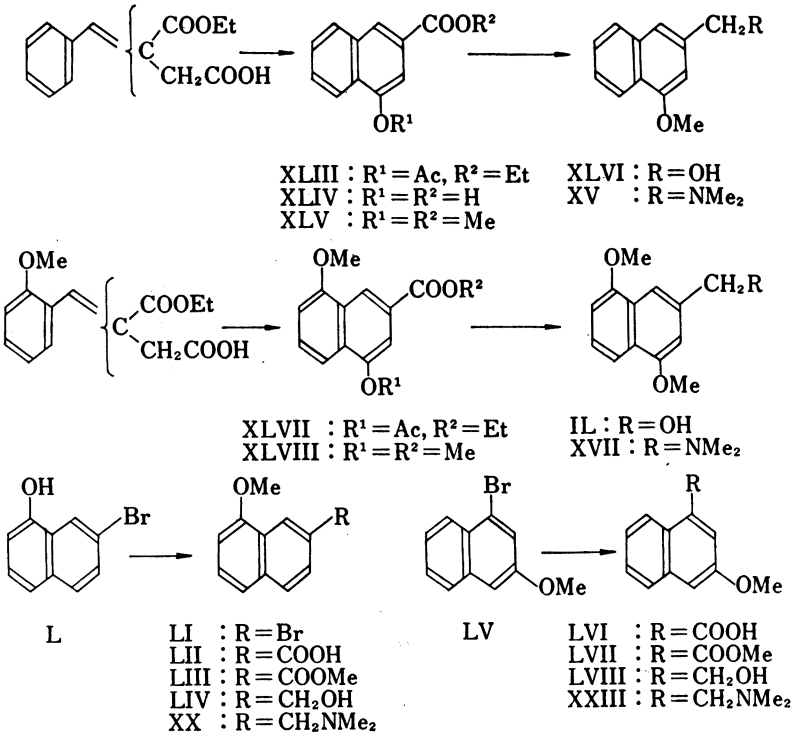


Chart 6

16) Dimethyl ethers of α- and β-sorigenin have been synthesized: *a*) Z. Horii, Y. Tamura, and T. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **10**, 893 (1962); *b*) Ref. 15.

17) The modified Stobbe condensation procedure by Horning, *et al.* was employed without hydrolysis of the resulting half ester [E.C. Horning and G.N. Walker, *J. Am. Chem. Soc.*, **74**, 5148 (1952)].

18) The acid (XLIV) has been prepared: *a*) From 4-amino-2-naphthoic acid, *b*) from 2-carboxynaphthalene-3,4-diazo-oxide, *c*) From 4-amino-2-naphthonitrile, and *d*) from 3-bromo-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid; *a*) C. Butler and F.A. Royle, *J. Chem. Soc.*, **123**, 1649 (1923); *b*) W. Luce and E.Runne, D.R.P. 523,358 (1928) [*Chem. Zentr.*, **1931 II**, 1635]; *c*) J. Cason, *J. Am. Chem. Soc.*, **63**, 828 (1941); *d*) R.D. Haworth, B. Jones, and Y.M. Way, *J. Chem. Soc.*, **1943**, 10.

benzylidenesuccinate was subjected to cyclization[19] with acetic anhydride along with sodium acetate in boiling acetic acid to give, in 43% yield, XLIII under recovery of the unaffected *trans*-isomer. Bromination of XLVI with phosphorous tribromide followed by treatment with alcoholic dimethylamine gave XV in 41% yield.

The dimethoxy-amine (XVII) was synthesized analogously from ethyl hydrogen 2-methoxybenzylidenesuccinate[17] *via* an acetoxynaphthoate[20] (XLVII), a dimethoxy-naphthoate[20] (XLVIII), and a dimethoxy-carbinol (IL). Conversion of IL into XVII was achieved in 81% yield.

The 8-methoxy-amine (XX) was synthesized from a bromonaphthol[21] (L) by 5-step procedure as described below. Methylation of L with dimethyl sulfate gave a methoxynaphthalene (LI), which was transformed, in 92% yield, into a naphthoic acid[22] (LII) through the Grignard reaction with carbon dioxide. Lithium aluminum hydride reduction of the methyl ester[23] (LIII) gave quantitatively a carbinol[24] (LIV), which was brominated[24] with phosphorous tribromide and subsequently condensed with dimethylamine to give XX in 67% yield.

The 3-methoxy-amine (XXIII) was synthesized from 1-bromo-3-methoxynaphthalene[25] (LV) by 4-step procedure *via* a 3-methoxynaphthoic acid[26] (LVI), a 3-methoxynaphthoate (LVII), and a 1-naphthalenemethanol[27] (LVIII).

Experimental[28]

Preparation of Ring-Methoxylated N,N-Dimethylnaphthalenemethylamines

Ethyl 4-Acetoxy-2-naphthoate (XLIII)——A mixture of *cis*- and *trans*-ethyl hydrogen benzylidenesuccinate was obtained as a brownish viscous oil in 49% yield by following the Horning's procedure.[17] A mixture of the half ester (50 g), AcOH (565 ml), Ac_2O (565 ml) and AcONa (17.5 g) was refluxed for 3 hr. Acetic acid and Ac_2O were removed *in vacuo*, and the residue was heated with 5% $NaHCO_3$ (500 ml) on a steam bath for 20 min. The undissolved material was taken in ether (150 ml × 3), and the ethereal extract was washed with satd. NaCl, dried and evaporated to give a brownish viscous oil (28 g), which was fractionated to give 25g (43%) of XLIII as yellowish crystals, mp 79—81°, bp 184—195° (4 mmHg). *Anal.* Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 70.19; H, 5.56. IR ν_{max}^{KBr} cm^{-1}: 1764 (OCOMe), 1706 (COOEt).

4-Hydroxy-2-naphthoic Acid[18] (XLIV)——A solution of XLIII (22.6 g) and 40% KOH (40 ml) in EtOH (40 ml) was refluxed for 3 hr. After evaporation of EtOH, the aqueous solution was filtered and acidified with conc. HCl to give crystals (14 g), mp 203—209°, which was recrystallized from benzene to give 12 g (70%) of XLIV as colorless crystals, mp 215—220° (lit.,[18b] mp 224—225°; lit.,[18c] mp 225—226°; lit.,[18d] mp 220—222°). IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH), 1678 (C=O).

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19) The procedure is in accordance with Johnson's method [W.S. Johnson and A. Goldman, *J. Am. Chem. Soc.*, **67**, 430 (1945)].

20) Similar cyclization of half methyl ester has been reported by El-Abbady, *et al.* [A.M. El-Abbady and L. S. El-Assal, *J. Chem. Soc.*, **1959**, 1024].

21) *a*) J. Franzen and S.B. Binkley, *J. Org. Chem.*, **24**, 992 (1959); *b*) R.C. Fuson, *J. Am. Chem. Soc.*, **47**, 516 (1925).

22) A preparation from 8-amino-2-naphthoic acid has been described by Girardet [A. Girardet, *Helv. Chim. Acta*, **14**, 516 (1931)].

23) The ester (LIII) has been reported by Girardet[22] without any description of experimental detail.

24) A lithium aluminum hydride reduction of the naphthoic acid (LII) and subsequent transformation into a naphthalenemethyl bromide using hydrobromic acid has been reported by Schreiber, *et al.* [K.C. Schreiber and R.C. Byers, *J. Am. Chem. Soc.*, **84**, 859 (1962)].

25) H.H. Hodgson and S. Birtwell, *J. Chem. Soc.*, **1943**, 468.

26) A preparation by methylation of 3-hydroxy-1-naphthoic acid has been described by Lesser, *et al.* [R. Lesser and G. Gad, *Ber*, **58**, 2551 (1925)].

27) Conversion of LVI into LVIII *via* an α-naphthaldehyde and subsequent transformation into a naphthalenemethyl bromide had been reported by Shoesmith, *et al.* [J.B. Shoesmith and H. Rubli, *J. Chem. Soc.*, **1927**, 3098].

28) Melting points and boiling points are uncorrected. Organic extracts were dried over anhyd. Na_2SO_4. The NMR spectra were measured at 60 Mc with tetramethylsilane as internal reference.

Methyl 4-Methoxy-2-naphthoate (XLV)——A suspension consisting of XLIV (45 g), anhyd. K_2CO_3 (220 g), Me_2SO_4 (120 ml) and dry acetone (800 ml) was refluxed for 12 hr. After removal of acetone, H_2O (800 ml) was added to the residual mass, followed by addifon of 14% NH_3 to destroy the excess Me_2SO_4. The mixture was extracted with benzene (200 ml×3). The extract was washed with 5% NH_3 and with H_2O, dried and evaporated. Fractionation of the residual oil gave 45 g (87%) of XLV as colorless oil, bp 160° (2 mmHg). *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.06; H, 5.66. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1692 (C=O).

4-Methoxy-2-naphthalenemethanol (XLVI)——To a suspension of $LiAlH_4$ (7.5 g) in dry ether (200 ml) was added a solution of XLV (41 g) in dry ether (200 ml) over 1 hr, and the suspension was refluxed for 1 hr. After destroying excess $LiAlH_4$ with AcOEt, the mixture was acidified with 10% H_2SO_4. The ethereal layer was separated, and the aqueous layer was extracted with ether (50 ml×2). The combined extract was shaken with satd. $NaHCO_3$ and with satd. NaCl, dried and evaporated to give 38 g (quantitative yield) of XLVI as colorless crystals, mp 47.5—48.5°, bp 145° (0.01 mmHg). *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.61; H, 6.26. IR ν_{max}^{KBr} cm^{-1}: 3270 (OH).

N,N-Dimethyl-4-methoxy-2-naphthalenemethylamine (XV)——To a solution of PBr_3 (62 g) in dry ether (350 ml) was added a solution of XLVI (36 g) in dry ether (200 ml) with stirring at −50——60° over 1 hr, followed by stirring at 0—10° for 6 hr. After concentration to one fifth of its volume below 25°, the residual liquid was added to a solution of Me_2NH (90 g) in anhyd. EtOH (400 ml) under ice-cooling over 30 min, followed by standing overnight at room temperature. After removal of the solvent, the residue was poured into ice-water (1 liter), followed by addition of 20% NaOH (200 ml). The mixture was extracted with ether (300 ml×3). The extract was washed with satd. NaCl, dried, evaporated and fractionated to give 17 g (41%) of XV as colorless oil, bp 135—139° (3 mmHg). Hydrogen oxalate: coloreless crystals, mp 178—179°, from EtOH. *Anal.* Calcd. for $C_{14}H_{17}ON \cdot C_2H_2O_4$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.10; H, 6.35; N, 4.82.

Ethyl 4-Acetoxy-8-methoxy-2-naphthoate (XLVII)——A mixture of *cis*- and *trans*-ethyl hydrogen *o*-methoxybenzylidenesuccinate was obtained as a pale brown semi-solid in 65% yield by following the Horning's procedure.[17] The half ester (82 g) was cyclized in a similar manner to that for XLIII to give yellowish crystals (42 g), mp 93—98°, which were recrystallized from EtOH to give 37 g (40%) of XLVII as pale yellow prisms, mp 100—102°. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.69; H, 5.49. IR ν_{max}^{KBr} cm^{-1}: 1764 (OAc), 1704 (COOEt).

Methyl 4,8-Dimethoxy-2-naphthoate[20] (XLVIII)——The acetoxy-ester (XLVII) was hydrolyzed in a similar manner to that for XLIV to give, in 64% yield, the hydroxy acid as colorless crystals (from AcOH), mp 253—255° (lit.[20] mp 259—260°). The acid (79 g) was methylated in a similar manner to that for XLV to give XLVIII (70 g, 81%) as colorless crystals, mp 105—106° (lit.[20] mp 107—108°). IR ν_{max}^{KBr} cm^{-1}: 1709 (C=O).

4,8-Dimethoxy-2-naphthalenemethanol (IL)——The ester (XLVIII, 68 g) in dry tetrahydrofuran (250 ml) was reduced with $LiAlH_4$ (11.2 g) in dry ether (300 ml) in a similar manner to that for XLVI to give 59 g (95%) of IL as coloress needles (from CCl_4), mp 137.5—138.5°. *Anal.* Clacd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.53; H, 6.30. IR ν_{max}^{KBr} cm^{-1}: 3205 (OH).

N,N-Dimethyl-4,8-dimethoxy-2-naphthalenemethylamine (XVII)——The carbinol (IL, 54 g) in dry tetrahydrofuran (300 ml) was brominated with PBr_3 (82 g) in dry ether (400 ml) in a similar manner to that for XV, followed by treatment with Me_2NH (120 g) in anhyd. EtOH. After working-up in a usual manner, there was obtained 84 g of a brownish oil, which was fractionated to give 55 g (81%) of XVII as colorless crystals, mp 65—65.5°, bp 160—165° (0.2 mmHg). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.07; H, 7.92; N, 5.77. NMR (in CCl_4) τ: 2.25 (1H, d, J=8.6 cps, C_3-H), 2.40 (1H, s, C_1-H), 2.78 (1H, t, J=8.6 cps, C_6-H), 3.13 (1H, s, C_3-H), 3.31 (1H, d, J=8.6 cps, C_7-H), 6.02 (3H, s, OMe), 6.09 (3H, s, OMe), 6.52 (2H, s, Ar-CH_2N), 7.79 (6H, s, NMe_2).

2-Bromo-8-methoxynaphthalene (LI)——7-Bromo-3,4-dihydro-1(2*H*)naphthalenone[29] was converted, in 79% yield, into 7-bromo-1-naphthol (L) by following the Franzen's method.[21a] The naphthol (L, 93 g) was methylated with Me_2SO_4 in 20% KOH in a usual manner to give 84 g (85%) of LI as colorless oil, bp 155—158° (8 mmHg). *Anal.* Calcd. for $C_{11}H_9OBr$: C, 55.72; H, 3.78. Found: C, 55.99; H, 4.06.

8-Methoxy-2-naphthoic Acid[22] (LII)——A Grignard reagent prepared from LI (83 g), EtBr (38.2 g) and Mg (17 g) in dry ether (200 ml) along with dry benzene (150 ml) was treated with dry ice (1.5 kg), and worked up in a usual manner to give 65 g (92%) of LII as colorless needles, mp 207—210° (lit.[22] mp 214°). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O).

Methyl 8-Methoxy-2-naphthoate[23] (LIII)——The acid (LII, 64 g) was methylated with Me_2SO_4 (80 g) in the presence of K_2CO_3 (220 g) in dry acetone (1 liter) by 9 hr's refluxing followed by a usual working-up as described for XLV to give 62 g (91%) of LIII as colorless oil, bp 171—175° (3 mmHg) (lit.[22] mp 72°), which solidified on standing. *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.53; H, 5.60. IR ν_{max}^{KBr} cm^{-1}: 1709 (C=O). NMR (in CCl_4) τ: 1.02 (1H, d, J=1.7 cps, C_1-H), 1.96 (1H, d of d, J=8.6 cps,

29) L.F. Fieser and A.M. Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938).

1.7 cps, C_3-H), 2.28 (1H, d, J=8.6 cps, C_4-H), 3.22 (1H, d of d, J=6 cps, 3.5 cps, C_7-H), 6.04 (3H, s, OMe), 6.10 (3H, s, OMe).

8-Methoxy-2-naphthalenemethanol[24] (LIV)——The ester (LIII, 45 g) was reduced with $LiAlH_4$ in a similar manner to that for XLVI to give 40 g (quantitative yield) of LIV as colorless crystals, mp 60—63° (lit.[24] mp 64—65°). IR ν_{max}^{KBr} cm^{-1}: 3260 (OH).

N,N-Dimethyl-8-methoxy-2-naphthalenemethylamine (XX)——The carbinol (LIV, 39 g) was converted into XX (30 g, 67%) in a similar manner to that for XV. Colorless oil, bp 173—175° (8 mmHg). *Anal.* Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.20; H, 7.93; N, 6.34. NMR (in CCl_4) τ: 1.88 (1H, broad singlet, C_1-H), 3.30 (1H, d of d, J=6 cps, 3 cps, C_7-H), 6.07 (3H, s, OMe), 6.47 (2H, s, $ArCH_2N$), 7.80 (6H, s, NMe_2).

3-Methoxy-1-naphthoic Acid[26] (LVI)——4-Bromo-2-naphthol, obtained, in 73% yield, by reduction of 4-bromonaphthalene-1,2-diazo-oxide[30] with sodium hydrosulfite, was methylated[25] to give 1-bromo-3-methoxynaphthalene (LV). The bromide (LV, 39 g) was converted, *via* a Grignard reagent, into LVI (26 g, 78%) in a similar manner to that for LII. Colorless crystals, mp 154—156° (lit.[26] mp 159°). IR ν_{max}^{KBr} cm^{-1}: 1685 (C=O).

Methyl 3-Methoxy-1-naphthoate (LVII)——The acid (LVI, 25 g) was methylated with CH_2N_2 in ether in a usual manner to give 27 g (98%) of LVII as colorless oil, bp 140—141° (3 mmHg). *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.01; H, 5.68. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1712 (C=O).

3-Methoxy-1-naphthalenemethanol[27] (LVIII)——The ester (LVII, 26 g) was reduced with $LiAlH_4$ in a similar manner to that for XLVI to give 21.5 g (98%) of LVIII as colorless crystals, mp 88° (lit.[27] mp 88°). IR ν_{max}^{KBr} cm^{-1}: 3290 (OH).

N,N-Dimethyl-3-methoxy-1-naphthalenemethylamine (XXIII)——The carbinol (LVIII, 21 g) was converted into XXIII (18 g, 69%) in a similar manner to that for XV. Colorless oil, bp 142—145° (3 mmHg). *Anal.* Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.30; H, 7.83; N, 6.38.

Lithiation

Methyl 2-(Dimethylaminomethyl)benzoate (VII)——To a BuLi solution, prepared from Li (1.6 g, 0.23 mole) and BuBr (13.0 g, 0.095 mole) in dry ether (50 ml), was added N,N-dimethylbenzylamine (IV, 5 g, 0.04 mole), followed by standing at room temperature for 20 hr. The reddish-brown mixture was poured onto cracked dry ice (50 g). The deposited white lithium salt was collected, washed with ether and dissolved in H_2O (30 ml). After removal of insoluble inorganic salt, mainly Li_2CO_3, the solution was passed through a column of Amberlite IRA-400 (OH^- form). The ion exchange resin was poured into H_2O, and washed repeatedly with H_2O until the washings became free from lithium ion, and subsequently with 1% HCl until the washings became acidic to methyl orange. The acid washings were combined and evaporated to dryness under reduced pressure, affording a pasty solid (3 g), which was dissolved in anhyd. MeOH (30 ml) and treated with excess of CH_2N_2 in ether. The solution was evaporated under reduced pressure, and the residue was washed with ether (20 ml × 3). The ethereal washings were evaporated to give a brownish oil (2.7 g), which on fractionation gave 2.5 g (35%) of VII as colorelss oil, bp 103° (3 mmHg). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82. Found: C, 68.31; H, 7.78. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1718 (C=O).

N-Methylnaphthalimide (VIII)——To a BuLi solution, prepared from BuBr (6.9 g, 0.05 mole) and excess Li in ether (50 ml), was added N,N-dimethyl-1-naphthalenemethylamine (V, 4 g, 0.02 mole), followed by standing at room temperature for 20 hr. On similar working-up to that for VII, there was obtained 2.8 g of a brownish oil, which solidified on standing for a few days and was chromatographed on silica gel in $CHCl_3$ to give 2.6 g (57%) of VIII as slightly brownish needles (from EtOH), mp 205—206°. *Anal.* Calcd. for $C_{13}H_9O_2N$: C, 73.92; H, 4.30; N, 6.63. Found: C, 73.58; H, 4.21; N, 6.56. IR ν_{max}^{KBr} cm^{-1}: 1707, 1661 (C=O), 1626, 1595 (arom.). NMR (in $CDCl_3$) τ: 1.48 (2H, d of d, J=7.2 cps, 1.2 cps, C_2-H, C_7-H), 1.87 (2H, d of d, J=8.5 cps, 1.2 cps, C_4-H, C_5-H), 2.32 (2H, quartet, J=8.5 cps, 7.2 cps, C_3-H, C_6-H), 6.50 (3H, s, N-Me). Mass Spectrum *m/e*: 211 (M^+, base peak).

The product was shown to be identical with the sample, prepared alternatively,[6] by mixed melting point and IR comparison.

From the amino ester component (IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725 (C=O)), no single compound could be isolated.

N-Methylnaphthalimidine (X)——The amine (V, 5.2 g) was lithiated with 2 molar equivalents of BuLi, and carboxylated in a similar manner to that for VIII, giving 4.8 g of a brownish glass. The glass was extracted with boiling $CHCl_3$ (20 ml × 3), and the extract was concentrated to 20 ml and immediately chromatographed on silica gel in $CHCl_3$. After elution of forerunning VIII (0.2 g), there was obtained, from the second eluate, 3.4 g (57%) of X as a pale yellow oil, which solidified on standing. The crystals, mp 120—130°, failed to be recrystallized from most solvent due to its instability[31] in the air, which resulted in its immediate contamination with VIII (detected from TLC and IR band at 1707 cm^{-1}). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1645 (C=O), 1620, 1596 (arom.). NMR (in $CDCl_3$) τ: 1.69 (1H, d of d, J=7.3 cps, 1.3 cps, C_2-H), 2.11 (1H, d of d, J=

30) H. Hodgson and S. Birtwell, *J. Chem. Soc.*, **1943**, 321.

31) After 2 days' standing at room temperature, the product in the solid state was found to be contaminated with a considerable amount of VIII.

8.3 cps, 1.3 cps, C_4-H), 5.13 (2H, s, Ar-CH_2-N), 6.81 (3H, s, N-Me). Mass Spectrum *m/e*: 197 (M^+), 196 (M^+-H, base peak with a metastable ion peak at *m/e* 195).

Methyl 2-Dimethylaminomethyl-1-naphthoate (XI) and Methyl 3-Dimethylaminomethyl-2-naphthoate (XII)——The amine (VI, 7 g) was lithiated, carboxylated and methylated in a similar manner to that for VII to give 4.7 g (52%) of a mixture of XI and XII as colorless oil, bp 160—170° (0.08 mmHg), which was fractionated by preparative GLC.[32]

The fraction of shorter retention time gave 2.6 g (29%) of XI as colorless oil. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04. Found: C, 73.77; H, 6.98. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1729 (C=O). NMR (in $CDCl_3$) τ: 2.13 (3H, m, C_4,C_5,C_8-H), 2.53 (3H, m, C_3,C_6,C_7-H), 6.02 (3H, s, OMe), 6.41 (2H, s, Ar-CH_2-N), 7.80 (6H, s, NMe_2).

The fraction of longer retention time gave 2 g (23%) of XII as colorless oil, bp 130° (0.001 mmHg), which solidified on standing to crystals, mp 71—73°. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.76; H, 6.86; N, 5.72. IR ν_{max}^{KBr} cm^{-1}: 1713 (C=O); $\nu_{max}^{CCl_4}$ cm^{-1}: 1721. NMR (in $CDCl_3$) τ: 1.67 (1H, s, C_1-H), 2.17 (3H, m, C_4,C_5,C_8-H), 2.50 (2H, m, C_6,C_7-H), 6.07 (3H, s, OMe), 6.16 (2H, s, Ar-CH_2-N), 7.74 (6H, s, NMe_2).

In an alternative procedure consisting of Fischer's esterification of the amino acid mixture with anhyd. MeOH, there was obtained a mixture of an easily methylated ester and an amino acid resistant to methylation. The former was identical with XII, and the latter was methylated with CH_2N_2 in MeOH–ether to give an amino ester which was identical with XI.

Methyl 3-Dimethylaminomethyl-1-methoxy-2-naphthoate (XVI)——The amine (XV, 8 g) was lithiated with 1.2 molar equivalents of BuLi, and worked up in a similar manner to that for VII to give 6 g of a brownish oil, homogeneous on GLC analysis. Fractionation gave 5.7 g (56%) of XVI as colorless oil, bp 150° (0.02 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1721 (C=O). NMR (in CCl_4) τ: 1.95 (1H, m, C_8-H), 2.60 (1H, s, C_4-H), 6.04 (3H, s, OMe), 6.17 (3H, s, OMe), 6.49 (2H, s, Ar-CH_2-N), 7.81 (6H, s, NMe_2). Hydrogen oxalate: colorless crystals (from EtOH), mp 169—170°. *Anal.* Calcd. for $C_{18}H_{21}O_7N$: C, 59.49; H, 5.83; N, 3.86. Found: C, 59.32; H, 5.81; N, 3.63.

Methyl 3-Dimethylaminomethyl-1,5-dimethoxy-2-naphthoate (XVIII)——The amine (XVII, 10 g) was lithiated with 1.2 molar equivalents of BuLi, and worked up in a similar manner to that for VII to give 7 g of a brownish oil, homogeneous on GLC analysis. Fractionation gave 6.4 g (52%) of XVIII as colorless oil, bp 160° (0.005 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1733 (C=O). NMR (in CCl_4) τ: 2.20 (1H, s, C_4-H), 2.36 (1H, d of d, J=8.4 cps, 0.8 cps, C_8-H), 2.71 (1H, t, J=8.4 cps, C_7-H), 3.27 (1H, d of d, J=8.4 cps, 0.8 cps, C_6-H), 6.06 (6H, s, $(OMe)_2$), 6.17 (3H, s, OMe), 6.46 (2H, s, Ar-CH_2-N), 7.79 (6H, s, NMe_2).

Hydrogen Oxalate: Colorless crystals (from EtOH), mp 174—175°. *Anal.* Calcd. for $C_{19}H_{23}O_8N$: C, 58.01; H, 5.89; N, 3.56. Found: C, 58.23; H, 5.73; N, 3.52.

Methyl 3-Dimethylaminomethyl-5-methoxy-2-naphthoate (XXI)——The amine (XX, 15 g) was lithiated, carboxylated and methylated in a similar manner to that for XVIII to give 8.3 g of a brownish oil which showed two peaks with area-ratio of 7:1 on GLC analysis. After distillation, the resulting colorless oil, bp 145° (0.002 mmHg), was fractionated by preparative GLC. The major component of longer retention time was obtained in 38% yield (7.2 g), but the minor one (0.5 g) was shown, from NMR measurement, to be a mixture of two other components difficult to separate. *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.09; H, 7.05; N, 5.21. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1726 (C=O). NMR (in CCl_4) τ: 1.81 (1H, s, C_1- or C_4-H), 1.86 (1H, s, C_1-or C_4-H), 3.20 (1H, d of d, J=6 cps, 3 cps, C_6-H), 5.99 (3H, s, OMe), 6.12 (3H, s, OMe), 6.20 (2H, s, Ar-CH_2-N), 7.80 (6H, s, NMe_2).

Methyl 1-Dimethylaminomethyl-3-methoxy-2-naphthoate (XXIV)——The amine (XXIII, 10 g) was lithiated, carboxylated and methylated in a similar manner to that for XVIII to give 3.5 g (39%) of a colorless oil, bp 160° (0.001 mmHg), homogeneous on GLC analysis. *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.63; H, 6.89; N, 5.10. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1733 (C=O). NMR (in CCl_4) τ: 1.75 (1H, m, C_8-H), 3.00 (1H, s, C_4-H), 6.11 (3H, s, OMe), 6.17 (3H, s, OMe), 6.31 (2H, s, Ar-CH_2-N), 7.80 (6H, s, NMe_2).

Lactonization

Trimethyl(2-methoxycarbonylbenzyl)ammonium Iodide (XXV)——A solution of VII (530 mg) and MeI (0.2 ml) in MeCN (10 ml) was refluxed for 1 hr, and poured into dry ether (50 ml). The deposited crystals were recrystallized from MeOH–ether to give 700 mg (76%) of XXV as colorless needles, mp 176—178°. *Anal.* Calcd. for $C_{12}H_{18}O_2NI$: C, 43.00; H, 5.41; N, 4.18. Found: C, 43.07; H, 5.29; N, 4.12. IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O).

Phthalide (XXVI)——The methiodide (XXV, 200 mg) was heated at 200—210° for 30 min. After cooling, the resulting solid was extracted with ether (10 ml × 3). The extract was evaporated to give 46 mg (57%) of XXVI, which was identified with authentic sample by mixed melting point and IR comparison.

32) GLC fractionation was carried out by employing Varian Aerograph Model 700 on SE-30 column (Column size, 3/8 in 10 ft. Column packing, 10% SE-30 on 40—60 mesh Chromosorb W. Column temperature, 180°).

Trimethyl(1-methoxycarbonyl-2-naphthalenemethyl)ammonium Iodide (XXVII)——The amino ester (XI, 1 g) was quarternarized in a similar manner to that for XXV to give 1.5 g (96%) of XXVII as colorless crystals, mp 183—185°. *Anal.* Calcd. for $C_{16}H_{20}O_2NI$: C, 49.88; H, 5.23; N, 3.64. Found: C, 49.82; H, 5.26; N, 3.42. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O).

2-Hydroxymethyl-1-naphthoic Acid γ-Lactone[11] (XXVIII)——Pyrolysis of XXVII (450 mg) gave 170 mg (79%) of XXVIII as colorless prisms (from benzene), mp 155—156° (lit.[11a] mp 154°, lit.[11b] mp 152—153°). *Anal.* Calcd. for $C_{12}H_8O_2$: C, 78.25; H, 4.83. Found: C, 78.23; H, 4.46. NMR (in $CDCl_3$) τ: 1.07 (1H, m, C_8-H), 1.90 (1H, d, J=7.8 cps, C_4-H), 2.54 (1H, d, J=7.8 cps, C_3-H), 4.73 (2H, s, Ar-CH_2-O). IR ν_{max}^{KBr} cm^{-1}: 1736 (C=O).

Trimethyl(3-methoxycarbonyl-2-naphthalenemethyl)ammonium Iodide (XXIX)——The amino ester (XII, 200 mg) was quarternarized in a similar manner to that for XXV to give 310 mg (97%) of XXIX as colorless crystals (from MeOH–ether), mp 196—199°. *Anal.* Calcd. for $C_{16}H_{20}O_2NI$: C, 49.88; H, 5.23; N, 3.64. Found: C, 50.09; H, 5.21; N, 3.70. IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O).

3-Hydroxymethyl-2-naphthoic Acid γ-Lactone[12] (XXX)——Pyrolysis of XXIX (500 mg) gave 180 mg (76%) of XXX as pale yellow crystals (by sublimation), mp 205—207° (lit.[12] mp 206°). *Anal.* Calcd. for $C_{12}H_8O_2$: C, 78.25; H, 4.38. Found: C, 77.88; H, 4.27. IR ν_{max}^{KBr} cm^{-1}: 1748 (C=O). NMR (in $CDCl_3$)τ: 1.44 (1H, s, C_1-H), 2.06 (1H, s, C_4-H), 4.50 (2H, s, Ar-CH_2-O).

Trimethyl(4-methoxy-3-methoxycarbonyl-2-naphthalenemethyl)ammonium Iodide (XXXI)——Quarternarization of XVI (2 g) in a similar manner to that for XXV gave 3 g (99%) of XXXI as colorless crystals (from MeOH–ether), mp 177—178°. *Anal.* Calcd. for $C_{17}H_{22}O_3NI$: C, 49.16; H, 5.34; N, 3.37. Found: C, 49.39; H, 5.67; N, 3.51. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O).

3-Hydroxymethyl-1-methoxy-2-naphthioc Acid γ-Lactone[14] (XXXII) and 1-Hydroxy-3-hydroxymethyl-2-naphthoic Acid γ-Lactone[14,15] (XXXIII)——Pyrolysis of XXXI (2 g) gave 500 mg of crude lactone, which was chromatographed on silica gel in benzene. The first fraction gave 70 mg (7%) of XXXIII as colorless leaflets (from benzene), mp 225—226°. The $FeCl_3$ test: green in EtOH. *Anal.* Calcd. for $C_{12}H_8O_3$: C, 71.99; H. 4.03. Found: C, 71.74; H, 4.19. IR ν_{max}^{KBr} cm^{-1}: 3378 (OH), 1724 (C=O). The product was dentified with the authentic sample[14,15] by mixed melting point and IR comparison.

The second fraction gave 200 mg (19%) of XXXII as colorless needles (from benzene), mp 136—138°, which was identified with the authentic sample,[14] mp 138°, by mixed melting point and IR comparison. NMR (in $CDCl_3$) τ: 1.61 (1H, m, C_8-H), 2.52 (1H, d, J=1.5 cps, C_4-H), 4.63 (2H, d, J=1.5 cps, Ar-CH_2-O), 5.64 (3H, s, OMe).

Trimethyl(4,8-dimethoxy-3-methoxycarbonyl-2-naphthalenemethyl)ammonium Iodide (XXXIV)——Quarternarization of XVIII (2 g) in a similar manner to that for XXV gave quantitatively XXXIV (2.9 g) as colorless prisms (from iso-PrOH), mp 133—134°. *Anal.* Calcd. for $C_{18}H_{24}O_4NI \cdot 1/2H_2O$: C, 47.55; H, 5.50; N, 3.09. Found: C, 47.37; H, 5.46; N, 2.92. IR ν_{max}^{KBr} cm^{-1}: 1718 (C=O).

1,5-Dimethoxy-3-hydroxymethyl-2-naphthoic Acid γ-Lactone (XXXV) and 1-Hydroxy-3-hydroxymethyl-5-methoxy-2-naphthoic Acid γ-Lactone (XXXVI)——The methiodide (XXXIV) was pyrolyzed at 200—210°, cooled and extracted with $CHCl_3$ (10 ml × 3). The extract was concentrated and chromatographed on silica gel in $CHCl_3$. The first fraction gave 100 mg (9%) of XXXVI as colorless leaflets (from benzene), mp 196—199°. *Anal.* Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.79; H, 4.57. IR ν_{max}^{KBr} cm^{-1}: 3390 (OH), 1715 (C=O).

The second fraction gave 250 mg (21%) of XXXV as colorless needles (from MeOH), mp 146—148°. *Anal.* Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.64; H, 4.97. IR $\nu_{max}^{KBr}$$cm^{-1}$: 1748 (C=O). NMR (in $CDCl_3$) τ: 2.05 (1H, doublet with negligible *m*-coupling, J=7.5 cps, C_8-H), 2.13 (1H, s, C_4-H), 2.52 (1H, t, J=7.5 cps, C_7-H), 3.07 (1H, d, J=7.5 cps, C_6-H), 4.69 (2H, s, Ar-CH_2-O), 5.69 (3H, s, OMe), 6.02 (3H, s, OMe).

Trimethyl(3-methoxy-2-methoxycarbonyl-1-naphthalenemethyl)ammonium Iodide (XXXVII)——Quarternarization of XXIV (2 g) in a similar manner to that for XXV gave quantitatively XXXVII (3 g) as colorless crystals (from MeOH–ether), mp. 184°. *Anal.* Calcd. for $C_{17}H_{22}O_3NI \cdot 3/2H_2O$: C, 46.18; H, 5.69; N, 3.17. Found: C, 46.51; H, 5.34; N, 3.24. IR ν_{max}^{KBr} cm^{-1}: 1724 (C=O).

1-Hydroxymethyl-3-methoxy-2-naphthoic Acid γ-Lactone (XXXVIII) and 3-Hydroxy-1-hydroxymethyl-2-naphthoic Acid γ-Lactone (XXXIX)——a) Ffrom XXXVII: Pyrolysis of XXXVII (2 g) in a similar manner to that for XXXV gave 800 mg of crude lactone, which was chromatographed on silica gel in $CHCl_3$. The first fraction gave 60 mg (6%) of XXXIX as colorless needles (from benzene), mp 185—187°. *Anal.* Calcd. for $C_{13}H_8O_3 \cdot 1/6C_6H_6$: C, 73.24; H, 3.89. Found: C, 73.22; H, 4.03. IR ν_{max}^{KBr} cm^{-1}: 3410 (OH), 1730 (C=O).

The second fraction gave 160 mg (15%) of XXXVIII as colorless needles (from benzene), mp 153—154°. *Anal.* Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 73.04; H, 4.82. IR $\nu_{max}^{KBr}$$cm^{-1}$: 1764 (C=O). NMR (in D_6-acetone) τ: 2.61 (1H, s, C_4-H), 4.38 (2H, s, Ar-CH_2-O), 6.00 (3H, s, OMe).

b) From Ethobromide (XL): The amine (XXIV, 1.5 g) was converted into its ethobromide (XL, 500 mg) by 1 hr's refluxing with EtBr (3.7 g) in MeCN (30 ml), pyrolyzed and worked up as described in a) to give 14 mg (4% from ethobromide) of XXXIX and 97 mg(26% from ethobromide) of XXXVIII.

Trimethyl(8-methoxy-3-methoxycarbonyl-2-naphthalenemethyl)ammonium Iodide (XLI)——Quarternarization of XXI (1 g) in a similar manner to that for XXV gave quantitatively XLI (1.5 g) as colorless crystals (from MeOH–ether), mp 198—200°. *Anal.* Calcd. for $C_{17}H_{22}O_3NI \cdot 1/2H_2O$: C, 48.10; H, 5.46; N, 3.30. Found: C, 47.81; H, 5.44; N, 3.25. IR ν_{max}^{KBr} cm^{-1}: 1706 (C=O).

3-Hydroxymethyl-5-methoxy-2-naphthioc Acid γ-Lactone (XLII)——Pyrolysis of XLI (1 g) in a similar manner to that for XXXV gave 500 mg of crude lactone, which was chromatographed on silica gel in $CHCl_3$ to give 230 mg (44%) of XLII as colorless prisms (by sublimation), mp 194—195°. *Anal.* Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 73.13; H, 4.62. IR ν_{max}^{KBr} cm^{-1}: 1748 (C=O). NMR (in $CDCl_3$) τ: 1.52 (1H, s, C_1-H), 1.60 (1H, s, C_4-H), 2.98 (1H, d of d, J=6cps, 2.3 cps, C_6–H), 4.53 (2H, s, Ar-CH_2-O), 5.95 (3H, s, OMe).

Attempted Demethylation of XXXV with Tetramethylammonium Iodide——A mixture of XXXV (100 mg) and Me_4NI (100 mg) was heated at 200—210° for 30 min. After cooling, the mixture was washed with H_2O to remove Me_4NI, affording unchanged XXXV quantitatively without any contamination with a material of positive $FeCl_3$-test.

Methylation of XXXIII to XXXII——The hydroxy-naphthalide (XXXIII, 200 mg) was refluxed with MeI (3 ml) and K_2CO_3 (5 g) in dry acetone (20 ml) for 10 hr. After removal of the inorganic material, the acetone solution was evaporated, and resulting residue was triturated with benzene to give 200 mg of XXXII, which was identified with the sample, obtained by pyrolysis, by mixed melting point and IR comparison.

Demethylation of XXXVIII to XXXIX——A solution fo XXXVIII (100 mg) and conc. HCl (4 ml) in acetone (10 ml) was refluxed for 1 hr. After evaporation under reduced pressure, the resulting residue was crystallized from benzene to give 56 mg (60 %) of colorless needles, mp 185—187°, which were identified with XXXIX by mixed melting point and IR comparison.