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Synthesis of 1*H*-Pyrrolo[1,2-*a*]indole Derivatives. I. Synthesis of 6*H*-Isoindolo[2,1-*a*]indoles by the Harley-Mason Method[1]

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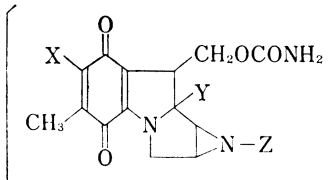
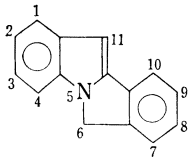
As an approach to the synthesis of mitomycin structure, 2-methoxy-10b,11-dihydro-6*H*-isoindolo[2,1-*a*]indole (X) and 2-methoxy-6*H*-isoindolo[2,1-*a*]indole (XI) were synthesized. By the oxidative cyclization of 1-(2,5-dihydroxybenzyl)isoindoline (VII) with alkaline potassium ferricyanide, a dihydroindole compound, 2-hydroxy-10b,11-dihydro-6*H*-isoindolo[2,1-*a*]indole (IX) was obtained as a main product beside a small amount of indole compound, 2-hydroxy-6*H*-isoindolo[2,1-*a*]indole (VIII).

Mitomycin[3] (I), an antitumor antibiotic complex, has a 1*H*-pyrrolo[1,2-*a*]indole ring system and several reports have already appeared regarding the synthesis of this ring system.[4] As an approach to the synthesis of this mitomycin structure, 6*H*-isoindolo[2,1-*a*]indoles (II), containing the said system, were synthesized in the present series of work by the application of the Harley–Mason method.[5] 2,3-Dimethoxy derivative of II had been synthesized by Sugasawa and Kanaoka[6] by the use of the Robinson dehydrogenation reaction.



I



II

mitomycin A : X=Y=OCH_3, Z=H
mitomycin B : X=OCH_3, Y=OH, Z=CH_3
mitomycin C : X=NH_2, Y=OCH_3, Z=H
porfiromycin : X=NH_2, Y=OCH_3, Z=CH_3

2,5-Dimethoxyphenylacetic acid[7] (III) was heated with an equimolar mixture of phthalic anhydride and sodium acetate to afford 2,5-dimethoxybenzalphthalide (IV), which in turn, was heated with an excess of formamide to form 3-(2,5-dimethoxybenzal)phthalimidine (V). V was electrolytically reduced to 1-(2,5-dimethoxybenzyl)isoindoline (VI), which was

1) Paper read at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.
2) Location: *No. 600, Kashiwagi 4-Chome, Shinjuku-ku, Tokyo, 160, Japan.*
3) T. Yamamoto and H. Umezawa Japan Patent 2898 (1956) [*C.A.* **51**, 9100 (1957)]; J.S. Webb, D. B. Cosulich, J.H. Mowat, J. B. Patrick, R.W. Broschard, W.E. Meyer, R.P. Williams, C.F. Wolf, W. Fulmor, C. P idacks, and J.B. Lancaster, *J. Am. Chem. Soc.*, **84**, 3185 (1962).
4) G.R. Allen, Jr., J.F. Poletto, and M.J. Weiss, *J. Org. Chem.*, **30**, 2897 (1965); G.R. Allen, Jr. and M.J. Weiss, *ibid.*, **30**, 2904 (1965); W.A. Remers, R.H. Roth, and M.J. Weiss, *ibid.*, **30**, 2910 (1965); Y. Yamada and M. Matsui, *Agr. Biol. Chem.* (Tokyo), **34**, 727 (1970); R.J. Friary, R.W. Franck, and J.F. Tobin, *Chem. Commun.*, **1970**, 283.
5) J. Harley-Mason and A.H. Jackson, *J. Chem. Soc.*, **1954**, 1165, 3651.
6) S. Sugasawa and Y. Kanaoka, *Chem. Pharm. Bull.* (Tokyo), **3**, 266 (1955).
7) L.F. Abbott and J.D. Smith, *J. Biol. Chem.*, **179**, 365 (1949).

demethylated by heating with 48% hydrobromic acid to 1-(2,5-dihydroxybenzyl)isoindoline (VII).

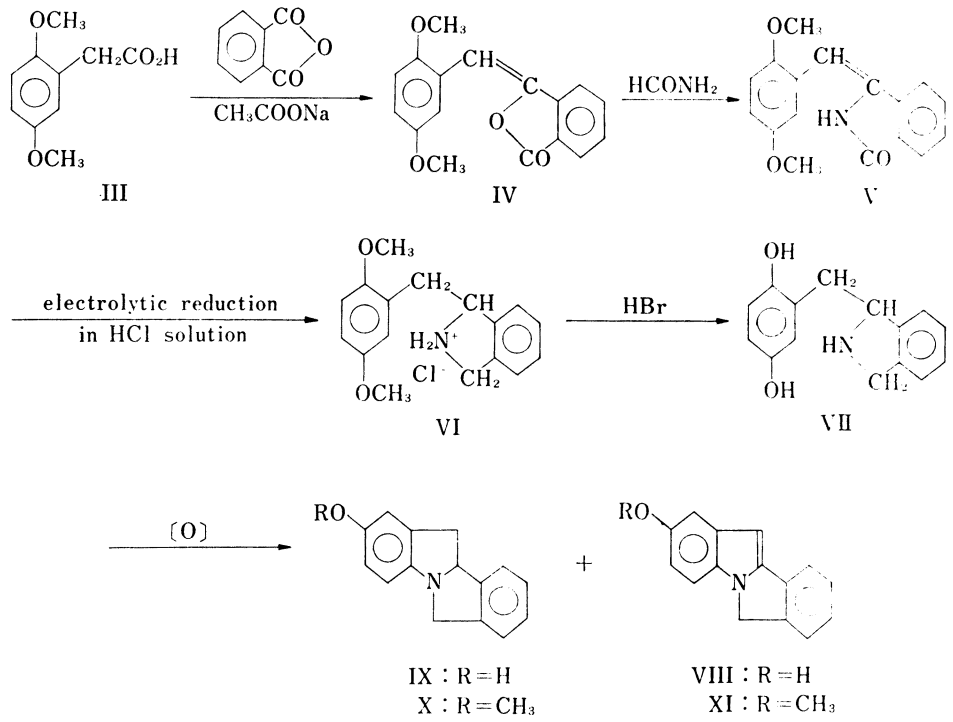


Chart 1

Harley-Mason and Jackson[5] obtained 5-hydroxyindole derivatives by the oxidation of 2-(2-aminoethyl)hydroquinones with alkaline potassium ferricyanide, and oxidative cyclization of VII under a similar condition was carried out. Recrystallization of the reaction product from benzene gave some crude crystals melting at *ca.* 200° whose separatory purification proved to be difficult. The product was purified by column chromatography, the portion giving a positive reaction with ferric chloride was collected, and purified to give a small amount of colorless needles, mp 204°. This product was considered to be 2-hydroxy-10b, 11-dihydro-6*H*-isoindolo[2,1-*a*]indole (IX) from its elemental analytical values and ultraviolet (UV) spectrum.

A part of the foregoing crude crystals of mp *ca.* 200° was also methylated with diazomethane and purified through chromatography, on which some colorless prisms, mp 83°, and a small amount of colorless plates, mp 214°, were obtained. The former was identified with 2-methoxy-10b,11-dihydro-6*H*-isoindolo[2,1-*a*]indole (X) and the latter with 2-methoxy-6*H*-isoindolo[2,1-*a*]indole (XI) from their elemental analyses, UV and nuclear magnetic resonance (NMR) spectra. Their yields from VII were not very good, being 22% in X and 0.75% in XI. X gradually changed into XI when its chloroform solution was allowed to stand for a long period of time.

Thus, this oxidative cyclization reaction unexpectedly afforded a dihydroindole compound (IX) besides a small amount of indole compound (VIII). Formation of IX was rather surprising because Harley-Mason and Jackson[5] had obtained 5-hydroxy-1-methylindole alone from N-methyl-2-(2,5-dihydroxyphenyl)ethylamine, and the fact that the dihydroindole compound (X) is quite easily oxidized to the indole compound (XI). The mechanism shown in

Chart 2 was presumed for this reaction with reference to the mechanism considered by Harley-Mason and Jackson, and that of Allen and others[8] on the Nenitzescu method, which is thought to be a similar reaction.

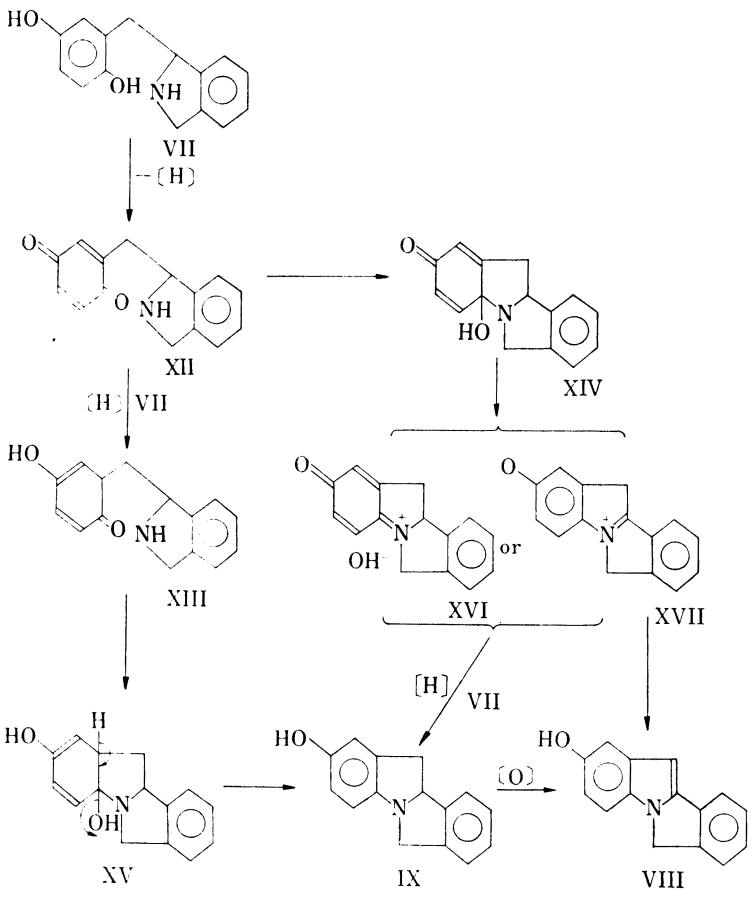


Chart 2

Both oxidation and reduction take part in the formation of IX. Reduction is thought to be effected by the disproportionation reaction between XII or XVI (or XVII) and VII. In the case of XVII, formation of VIII by intramolecular proton transfer may take place preferentially. If a quinoniminonium type like XVI were difficult to be formed,[9] a route *via* XIII could be considered.

Braun and Mecke[10] obtained 2,5-bis(2-carboxyanilino)-1,4-benzoquinone by the reaction of hydroquinone with anthranilic acid in the presence of sodium chlorate and a minute amount of ammonium vanadate. Oxidation of VII under the same conditions as those of Braun and Mecke was attempted in order to obtain the cyclized XVIII from VII *via* XII having a quinone structure, but the objective compound was not produced. It was found that 2-hydroxy-10b, 11-dihydro compound (IX) was also formed, as well as in the oxidation with alkaline ferricya-

8) G.R. Allen, Jr., C. Pidacks, and M.J. Weiss, *Chem. Ind.* (London), **1965**, 2096; *idem*, *J. Am. Chem. Soc.*, **88**, 2536 (1966).
9) *cf.* Y. Yamada and M. Matsui, *Agr. Biol. Chem.* (Tokyo), **34**, 727 (1970).
10) W. Braun and R. Mecke, *Chem. Ber.*, **99**, 1991 (1966).

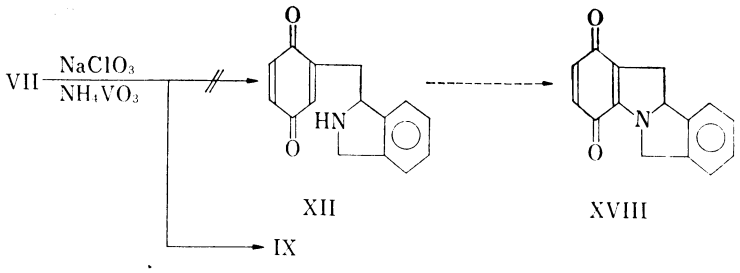


Chart 3

nide, and the structure of the product was confirmed by the melting point and infrared (IR) spectrum.

Thus, the Harley-Mason method will be generally applied to a synthesis of 5-hydroxyindole derivatives, which could be further converted into the indoloquinones by a milder oxidation.[11] Therefore, this Harley-Mason method would be effective for the synthesis of the fundamental skeleton of I, which is described in the following paper.

Experimental[12]

2,5-Dimethoxybenzalphthalide (IV)——A mixture of 13.2 g of 2,5-dimethoxyphenylacetic acid, 10.0 g of phthalic anhydride, and 0.56 g of anhyd. AcONa was heated at 255° (bath temp.) for 3 hr, on which the reaction proceeded with evolution of CO_2 and H_2O. When cooled, the reaction mixture was pulverized, parts soluble in NH_4OH were removed, and the residue was recrystallized from EtOH to 10.6 g (55%) of yellow prisms, mp 164°. *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.55; H, 4.90. IR ν_{max}^{KBr} cm^{-1}: 1770 (C=O), 1675 (C=C). UV λ_{max}^{EtOH} $m\mu$: 299, 379.

3-(2,5-Dimethoxybenzal)phthalimidine (V)——A mixture of 5.65 g of IV and 6 ml of $HCONH_2$ was heated gradually in an oil bath, on which the reaction started with effervescence. The mixture was heated at 190—195° (bath temp.) for 3 hr, allowed to cool, and H_2O was added to separate crystals. The product was collected, washed with water, and recrystallized from EtOH to 4.96 g (88%) of pale yellow needles, mp 170°. *Anal.* Calcd. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98. Found: C, 73.00; H, 5.34; N, 5.28. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O), 1670 (C=C).

1-(2,5-Dimethoxybenzyl)isoindoline Hydrochloride (VI)——A mixture of 5 g of V, 250 ml of MeOH, 250 ml of AcOH, and 50 ml of conc. HCl was used as the cathode solution and 20% H_2SO_4 as the anode solution, with lead plates (surface area, 100 cm^2) as the cathode, and submitted to electrolytic reduction at room temperature with a current of 3A for 4 hr. The cathode solution was evaporated to dryness on a water bath at a reduced pressure. The syrupy residue was dissolved in H_2O, basified with NaOH, and the precipitate was extracted with ether. The extract was dried over Na_2SO_4, ether was evaporated, and dry HCl gas was bubbled through the residual solution. The crystals that separated out were collected and recrystallized from EtOH+ether to 4.24 g (78%) of colorless prisms, mp 188° (decomp.). *Anal.* Calcd. for $C_{17}H_{20}O_2NCl$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.58; H, 6.86; N, 4.78.

1-(2,5-Dihydroxybenzyl)isoindoline (VII)——A mixture of 2 g of VI and 20 ml of 48% HBr was heated in an oil bath at 140—145° for 3 hr. The cooled reaction mixture was diluted with H_2O, basified with $NaHCO_3$, and extracted with AcOEt. The extract was dried over Na_2SO_4, AcOEt was evaporated under a reduced pressure at room temperature, and the residue was recrystallized from AcOEt to 1.50 g (95%) of colorless plates, mp 218° (decomp.) *Anal.* Calcd. for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.23; H, 6.63; N, 5.93.

2-Hydroxy-10b,11-dihydro-6*H*-isoindolo[2,1-*a*]indole (IX)——a) A solution of 2.63 g of $K_3Fe(CN)_6$ and 1.40 g of $NaHCO_3$ in 65 ml of H_2O was added dropwise over 45 min into a solution of 960 mg of V in 200 ml of AcOEt, being stirred at room temperature, and the whole was stirred for further 15 min. The solution turned dark brown with the dropwise addition of the alkaline $K_3Fe(CN)_6$. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated under a reduced pressure at room temperature. The residue was treated with benzene and the benzene-soluble portion (288 mg)

11) W.A. Remers, P.N. James, and M.J. Weiss, *J. Org. Chem.*, **28**, 1169 (1963).

12) All melting points are uncorrected. NMR spectra were measured by JNM 4H-100 (100 Mc) spectrophotometer and tetramethylsilane was used as internal reference. IR and UV spectra were measured on a JASCO DS-301 IR Spectrophotometer and on a Hitachi EPS-3 UV spectrophotometer, respectively.

was submitted to column chromatography over Al_2O_3. The column was eluted with $CHCl_3$ and the effluent giving bluish green coloration (142 mg) with $FeCl_3$ and that giving a blue coloration (77 mg) with the same reagent were collected separately. Majority of the former melted at 203—205°, and the remainder melted at *ca.* 250°, and this product was considered to be a mixture of VIII and IX. Further chromatographic separation failed to effect pure isolation of VIII. The product giving a blue coloration with $FeCl_3$ was repeatedly recrystallized from benzene and IX was obtained as colorless needles, mp 204°. *Anal.* Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.30; H, 5.85; N, 6.31. UV λ_{max}^{EtOH} mμ: 239, 311.

b) To a solution of 120 mg of V in 7 ml of aqueous 60% MeOH, containing a minute amount of NH_4VO_3, 240 mg of 50% $NaClO_3$ solution was added dropwise over 10 min with stirring at room temperature, the mixture was further stirred for 10 min, and MeOH was evaporated under a reduced pressure. The product was chromatographed over Al_2O_3, eluted with AcOEt, and the product was recrystallized from benzene to 14 mg of colorless needles, mp 204°. This was identified with IX through IR spectrum.

2-Methoxy-10b,11-dihydro-6*H*-isoindolo[2,1-*a*]indole (X) and 2-Methoxy-6*H*-isoindolo[2,1-*a*]indole (XI) ——The hot benzene-soluble portion (270 mg), obtained by the foregoing method (a) for the preparation of IX, was methylated with CH_2N_2 in EtOH by the conventional method and the product was purified through column chromatography over silica gel (benzene), affording XI and then X. Recrystallization of X from dil. EtOH gave 207 mg (22%) of colorless prisms, mp 83°. *Anal.* Calcd. for $C_{16}H_{15}ON$ (X): C, 80.98; H, 6.37; N, 5.90. Found: C, 80.71; H, 6.48; N, 6.09. UV λ_{max}^{EtOH} mμ: 240, 309. NMR ($CDCl_3$) τ: 2.72 (3H, multiplet, aromatic H), 3.25 (4H, singlet, aromatic H), 4.76 (1H, multiplet, N-CH=), 5.43 (2H, doublet of doublet, J=20 and 13 cps, N-CH_2-), 6.28 (3H, singlet, OCH_3), 6.58 (2H, doublet of doublet, J=15 and 10 cps, N-CH-CH_2-).

Recrystallization of XI from AcOEt gave 7 mg (0.75%) of colorless plates, mp 241°. *Anal.* Calcd. for $C_{16}H_{13}ON$ (XI): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.82; H, 5.67; N, 5.93. UV λ_{max}^{EtOH} mμ: 229, 259 (shoulder), 225, 340. NMR ($CDCl_3$) τ: 2.20—2.85 (7H, multiplet, aromatic H), 3.05 (1H, singlet, -CH=), 4.95 (2H, singlet, N-CH_2-), 6.12 (3H, singlet, -OCH_3).

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