SYNTHESIS OF PYRROLO[1,2-a]INDOLES AND RELATED SYSTEMS

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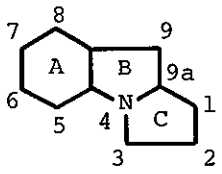
The various syntheses of pyrrolo[1,2-a]indoles and related compounds, which are the main framework of the mitomycins, are described.

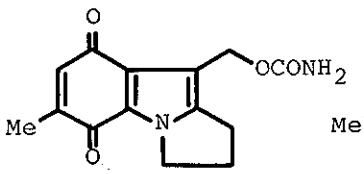
INTRODUCTION

The chemistry of the pyrrolo[1,2-a]indole (1) has progressed extensively since the structures of mitomycins (2) and (3) were determined by Webb and co-workers in 1962[1]. The mitomycins were isolated by Hata and co-workers[2] in 1956 and have attracted much attention not only because of their unique structures but also biological activity, e.g. antitumor activity in the case of mitomycin C. During their investigation on the structures of mitomycins, Webb and co-workers prepared the aziridinopyrrolo-[1,2-a]indoloquinone (4), the 1,2-disubstituted mitosene (5) and the desammono-apomitomycin A (6) from the natural mitomycins. Since these compounds were found to possess potent antibacterial properties, numerous compounds related to mitosane and mitosene[3] have been synthesized.[4]

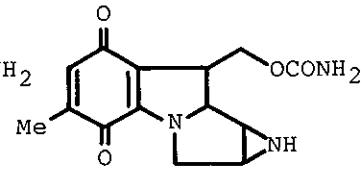
Chart 1



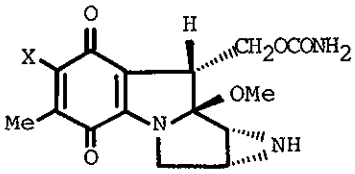
(1)



Mitosene

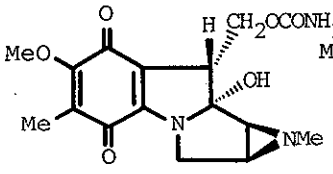


Mitosane



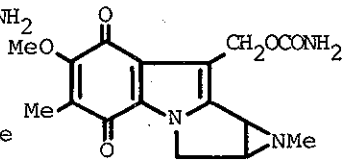
(2)

Mitomycin A X=OMe
Mitomycin C X=NH2



(3)

Mitomycin B



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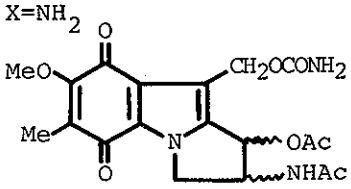

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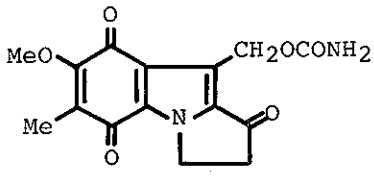
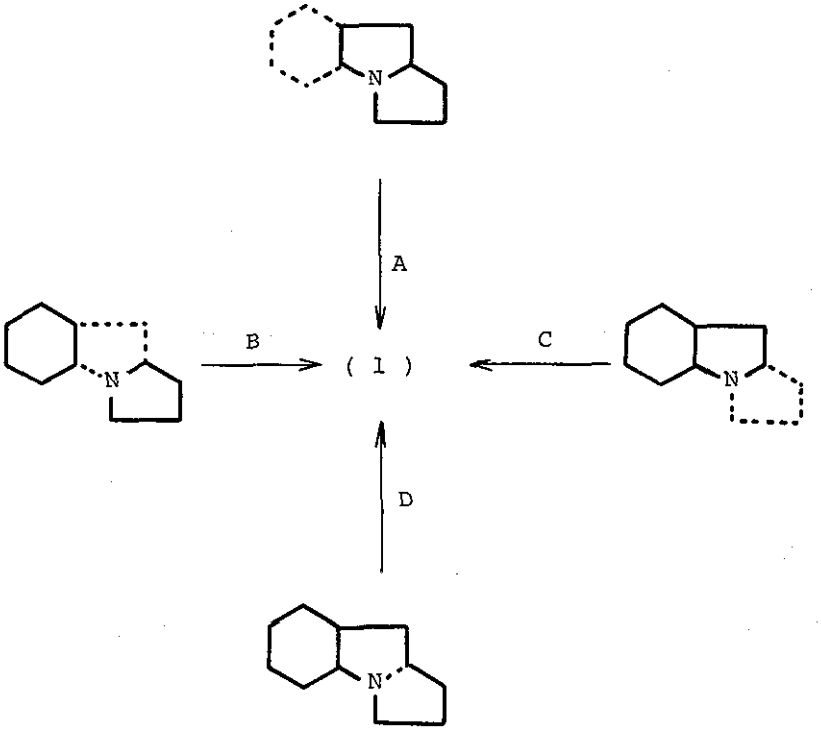


(6)

The procedures for the synthesis of pyrrolo[1,2-a]indole, which comprises the main framework of mitosane and mitosene, can be divided into four patterns: the first method (A) consists in a cyclization which makes ring A; the second method (B) and the third method (C) form ring B or ring C, respectively; the fourth method (D) is a transannular cyclization between the nitrogen atom and the C_{9a} carbon as the final step.

In this review, we wish to discuss the synthesis of pyrrolo-[1,2-a]indoles according to the above classification.

Chart 2



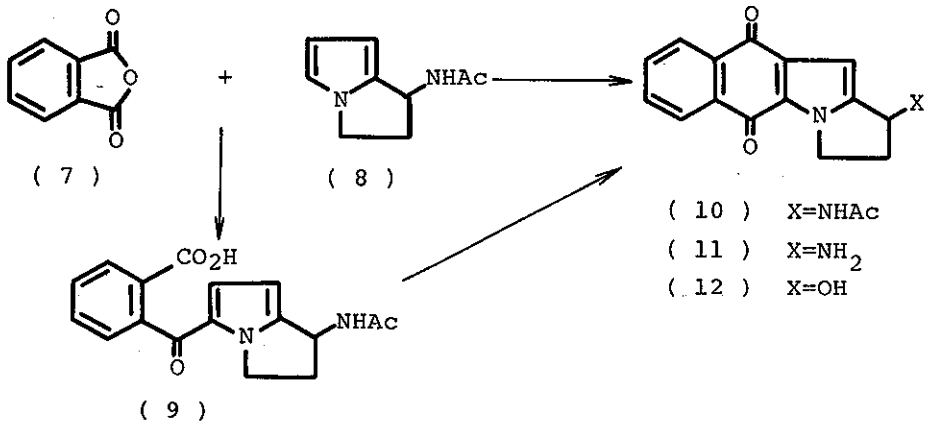
METHOD A

This method consists in the formation of the new bond either between the C_8 and C_{8a} positions by a Friedel-Crafts type reaction or between the C_7 and C_8 positions by Dieckmann cyclization.

Carelli and co-workers[5] have synthesized the quinone derivative (10), which has the related pyrrolo[1,2-a]indole system, by Friedel-Crafts reaction of pyrrole 8 with phthalic anhydride (7). Heating a mixture of 7 and 8 at 50-55° in nitrobenzene in the presence of aluminum chloride gave 9, while at 100-110°, 10 was formed. Compound 10 was also obtained when 9 was treated as above at

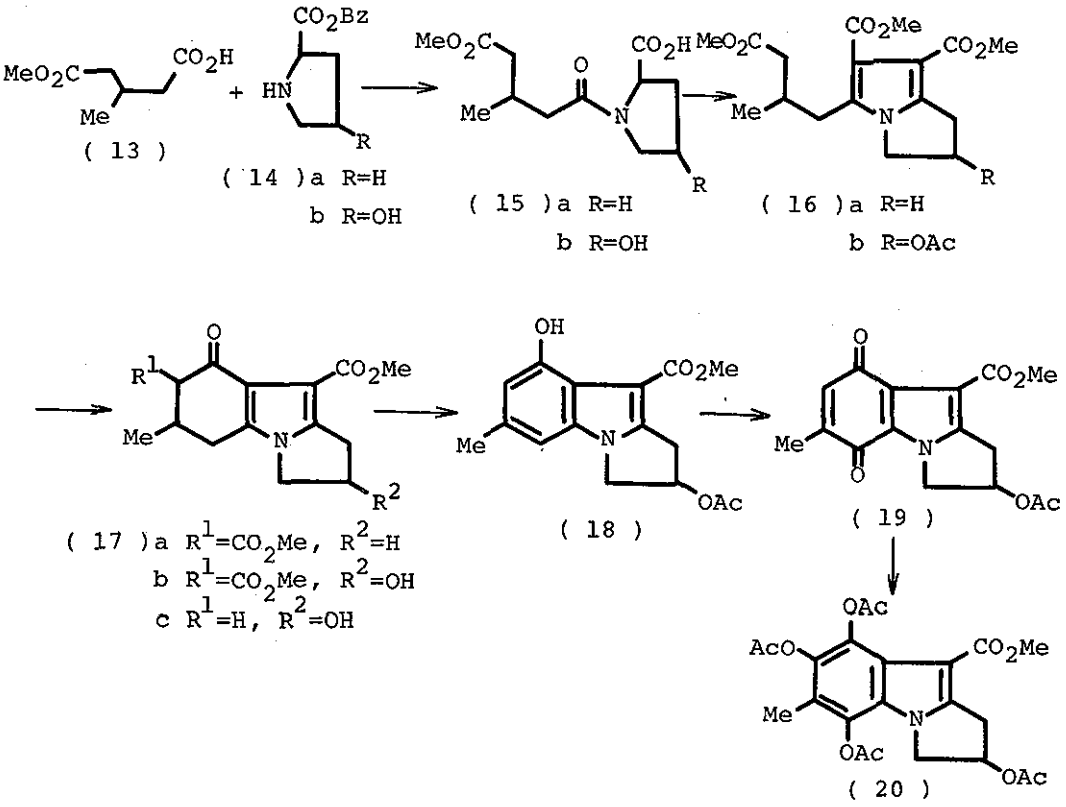
70-80°. Hydrolysis of the acetamido group of 10 to amine 11 followed by diazotization afforded the alcohol 12.

Chart 3



Recently, Rebek and Gehret have reported a synthesis of mitosene derivatives based on 1,3-dipolar cycloaddition to form the pyrrole (ring B) followed by Dieckmann cyclization to form the ring A of mitosene.[6] The glutaric derivative 13 was condensed with proline benzyl ester 14a and then debenzylated to give the carboxylic acid 15a. The pyrrole 16a was obtained by treatment of 15a in acetic anhydride containing dimethyl acetylenedicarboxylate. A parallel series of reactions, using L-hydroxyproline as starting material, gave 16b as a mixture of diastereoisomers. Dieckmann cyclization of 16 yielded the tricyclic diester 17a,b. Decarbomethoxylation of 17b followed by oxidation of 17c gave the optically active phenol 18 from which the quinone 19 could be obtained by Fremy's oxidation. Thiele acetoxylation of 19 gave the tetraacetate 20.

Chart 4



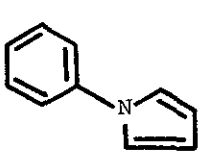
METHOD B

The second method involves bond formation between C_9-C_{9a}, C_{8a}-C_9, or N-C_{4a}, and is used widely in the synthesis of the pyrrolo[1,2-a]indole systems.

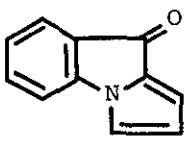
9-Keto-9H-pyrrolo[1,2-a]indole (22) was first isolated by Shirley and co-workers as a minor product from the carbonation of lithiated 1-phenylpyrrole (21).[7] Laschtuvka and Huisgen prepared the tricyclic ketone 22 by decarboxylation of the keto acid 25,

obtained from the Friedel-Crafts cyclization of 1-phenylpyrrole-2,3-dicarboxylic anhydride (24).[8] Wolff-Kishner reduction of the semicarbazone of 22 afforded the 9H-pyrrolo[1,2-a]indole (23).

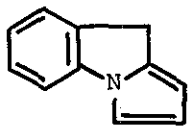
Chart 5



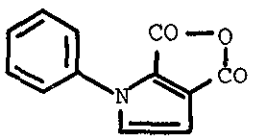
(21)



(22)



(23)



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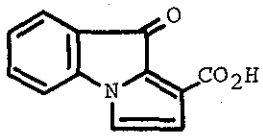
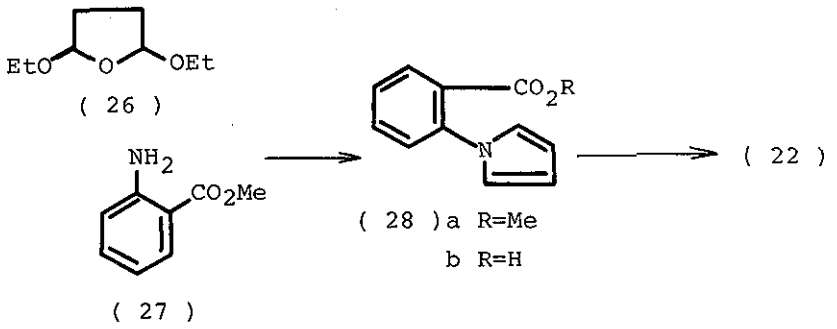


(25)

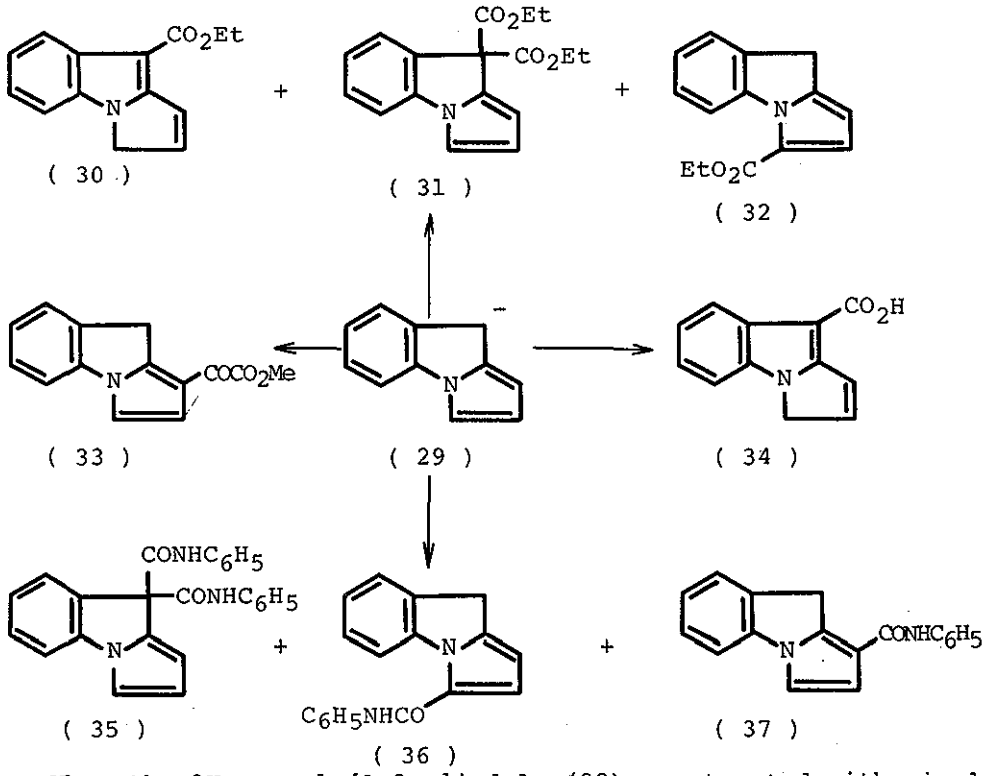
Josey and Jenner[9] synthesized ring B by forming the bond between the C_9 and C_{9a} positions. The pyrrole ester 28a was prepared by condensation of the amino ester 27 with 2,5-diethoxytetrahydrofuran (26) in acetic acid. Saponification of the ester 28a was accomplished with potassium hydroxide in ethylene glycol and then cyclization of the resulting acid 28b with polyphosphoric acid afforded the ketone 22. Modification of this methods by Franck and co-workers consisted of the saponification of the ester 28a with aqueous methanolic potassium hydroxide, most importantly, followed by the Friedel-Crafts cyclization on the acid chloride (derived by treating the acid 28b with phosphorus pentachloride) with stannic chloride as a catalyst.[10]

Chart 6



Some reactions were carried out to functionalize the pyrroloindole skeleton. The pyrrolo[1,2-a]indole anion 29 has been acylated by a group of electrophiles including ethyl carbonate, ethyl chloroformate, dimethyl oxalate, phenyl isocyanate, and carbon dioxide to give the acylated products as shown in Chart 7. Its tridentate character has been demonstrated by the isolation of products arising from the attack at the 1,3 and 9 positions.[11]

Chart 7



(30) + (31) + (32)

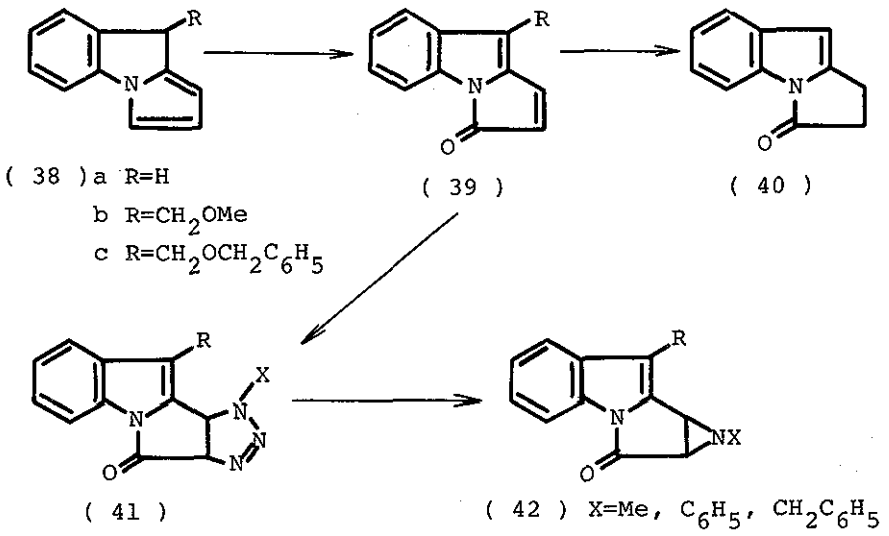
(33) (29) (34)

(35) + (36) + (37)

When the 9H-pyrrolo[1,2-a]indole (38) was treated with singlet oxygen, rapid oxygenation took place and the indole-lactam 39 was isolated.[12] Hydrogenation of 39 afforded 40 while cycloaddition of benzyl and phenyl azide to 39 provided 41 as the first step in the aziridine synthesis. The photochemical elimination of nitrogen proceeded smoothly to afford a quantitative yield of the aziridine 42. Alkylation of the anion 29 with chloromethyl methyl ether gave no isolable product since the crude reaction products decomposed during removal of the solvent. Therefore, alkylation of the anion 29 in solvent followed by photooxygenation afforded the 9-substituted 3-keto-3H-pyrrolo[1,2-a]indole (39b,c). Alkylations were carried out on the lithium derivatives with chloromethyl

methyl ether and chloromethyl benzyl ether. A variety of triazoles 41 were also prepared using the method described above. Their irradiation with a high pressure mercury lamp gave the aziridines 42.[13]

Chart 8



(38)a R=H
b R=CH_2OMe
c R=$CH_2OCH_2C_6H_5$

(39)

(40)

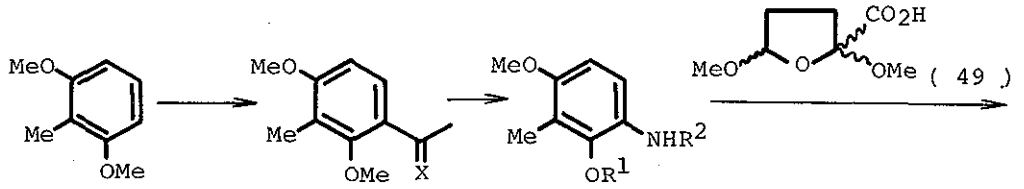
(41)

(42) X=Me, C_6H_5, $CH_2C_6H_5$

Franck and co-workers reported the synthesis of the pyrrolo-[1,2-a]indole (54) using a unique meta-photo-Fries reactions.[14] Nitrogen was indirectly introduced into 2,6-dimethoxytoluene (43) via acylation followed by Beckmann rearrangement of the oxime of the acetophenone 44. The acetanilide 46 could be demethylated using aluminum chloride in methylene chloride to afford the free phenol 47. Hydrolysis of 47 afforded the air-sensitive amine hydrochloride 48 which was condensed with the tetrahydrofuran 49 to yield the lactone 50. The lactone was nitrated to 51 which

was reduced to the amine 52 followed by acetylation to give 53. Irradiation of 53 with a sun-lamp through a plate-glass filter in tetrahydrofuran gave a clean and essentially quantitative yield of 54 rather than the isomer 55.

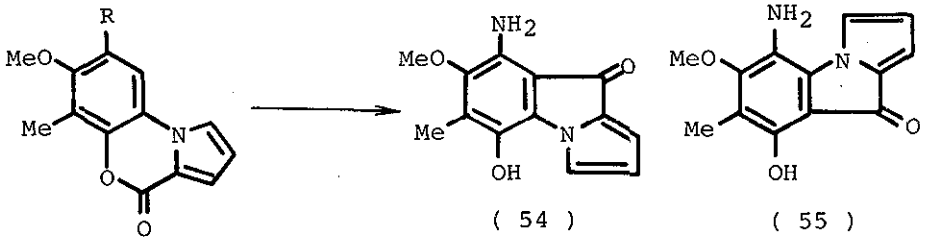
Chart 9



(43)

(44) X=O
(45) X=NOH

(46) R^1=Me, R^2=$COCH_3$
(47) R^1=H, R^2=$COCH_3$
(48) R^1=H, R^2=H·HCl



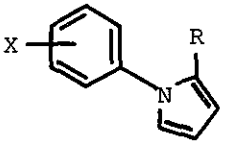
(54) (55)

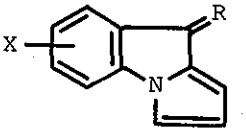
(50) R=H
(51) R=NO_2
(52) R=NH_2
(53) R=NHAc

Friedel-Crafts cyclization of the 1-phenyl-2-pyrrolecarboxylic acid chloride (61) gave, in good yields, the corresponding 9-keto-9H-pyrrolo[1,2-a]indoles (62) which were then converted into

the 9-hydroxy derivatives 63 or into the 9H-pyrrolo[1,2-a]indoles (64) by lithium aluminum hydride or Wolff-Kishner reduction. The synthesis of the acid chlorides 61 was achieved from 1-phenylpyrrole (56) as follows; formylation to the aldehyde 57, followed by conversion to the oxime 58, dehydration to 59, saponification to the acid 60 and chlorination with thionyl chloride.[15]

Chart 10





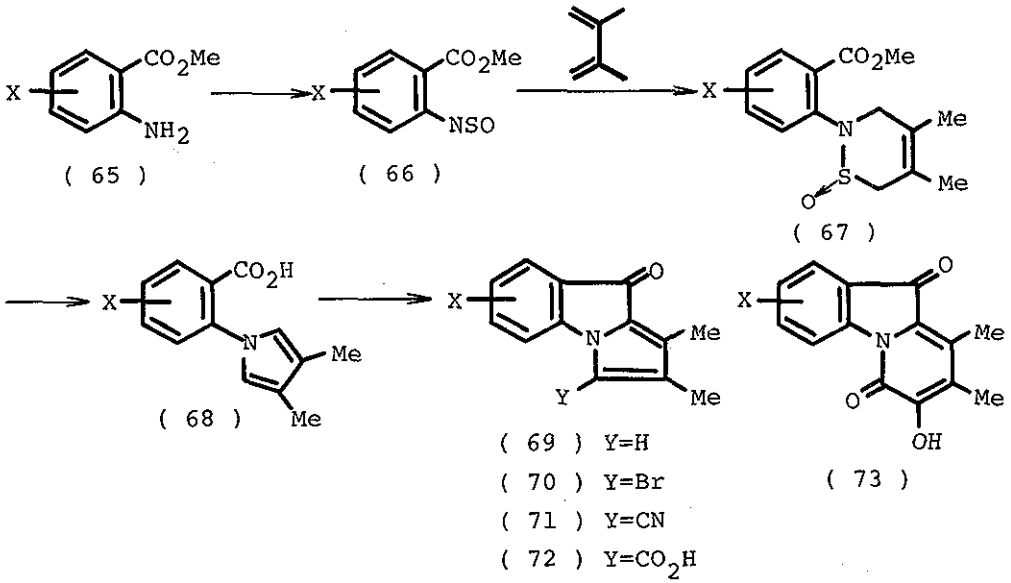
(56) R=H
(57) R=CHO
(58) R=CH=NOH
(59) R=CN
(60) R=CO_2H
(61) R=COCl

(62) R=O
(63) R=H, OH
(64) R=H_2

Sugihara and co-workers synthesized a number of pyrrolo-[1,2-a]indole derivatives in order to investigate the reactivity and pharmacological activity of this ring system.[16] Methyl anthranilate was converted to 1-(2-carboxyphenyl)-3,4-dimethyl-pyrrole (68) as shown in Chart 11. By treatment with acetic anhydride and acetic acid, 68 gave the 1,2-dimethyl-9H-pyrrolo-[1,2-a]indol-9-ones (69) in good yield. The 3-cyano derivatives 71 were synthesized *via* 70 by bromination of 69 with bromine followed by treatment with cuprous cyanide. Hydrolysis of 71 gave the

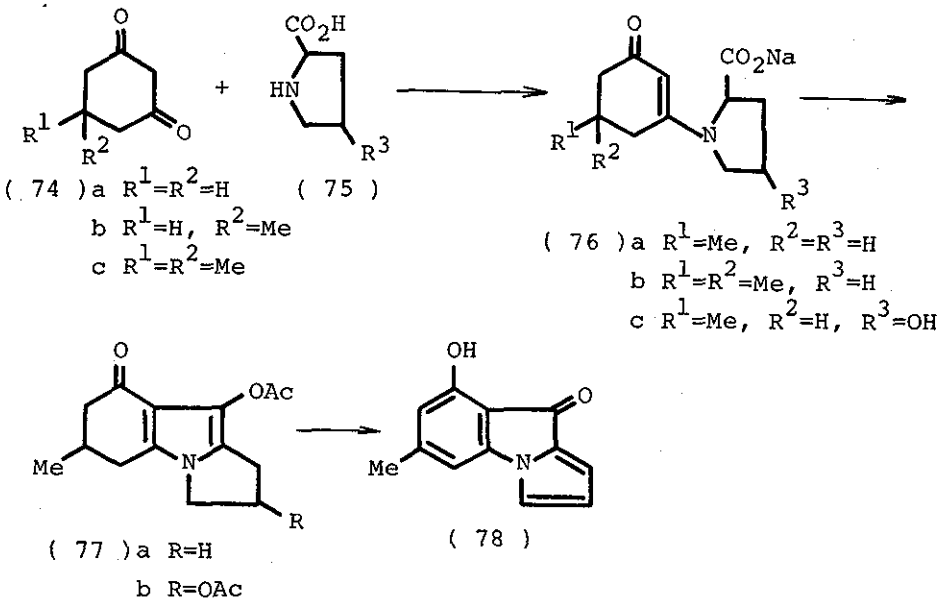
1,2-dimethyl-9-oxo-9H-pyrrolo[1,2-a]indole-3-carboxylic acids (72) as well as the rearranged products, whose structures were assigned as 6,10-dihydro-7-hydroxy-8,9-dimethylpyrido[1,2-a]-indole-6,9-diones (73) on the basis of spectroscopic properties.

Chart 11



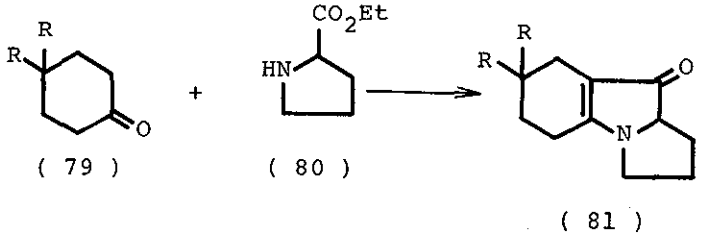
Franck and co-workers[17] described the incorporation of enamines derived from the reaction of natural amino acids 75 with cyclic diketones 74, into pyrrolo[1,2-a]indoles. Sodium salts of the amino acids, formed by treating the free acid with sodium hydride, were heated with the diketone in dimethylformamide. The product 76 was then cyclized in hot acetic anhydride to the desired 1,2,5,6,7,8-hexahydro-8-ketopyrrolo[1,2-a]indole (77) which on treatment with palladium charcoal in refluxing mesitylene afforded the completely aromatized compound 78.

Chart 12



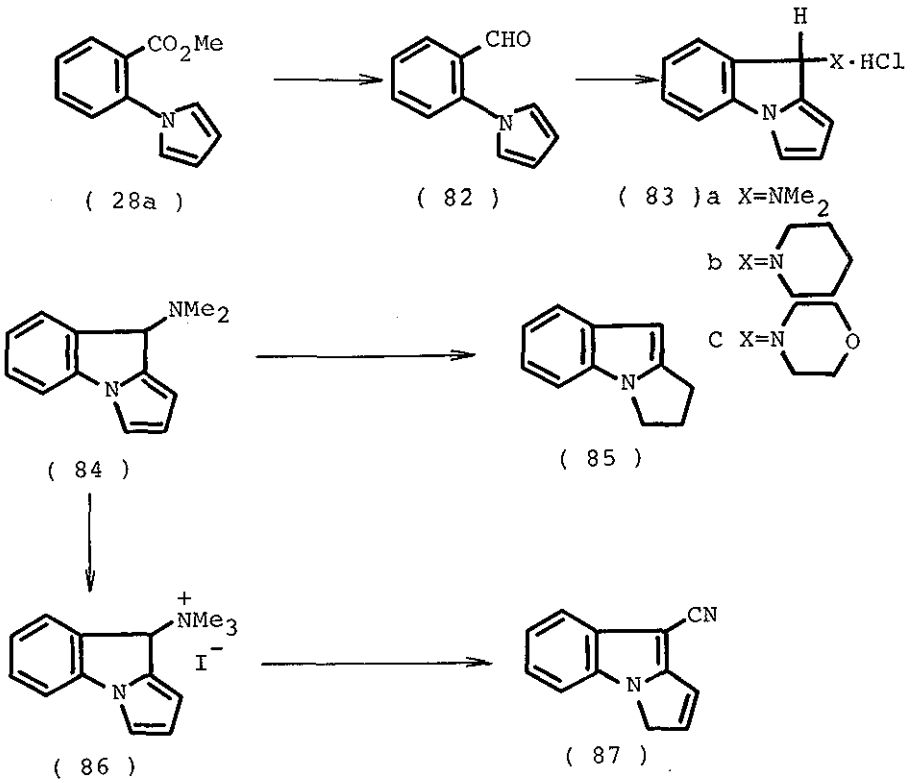
The related method to form the perhydropyrrolo[1,2-a]indoles (81) were reported by Hickmott and Woodward.[18] When the cyclohexanone derivatives 79 were heated with ethyl L-prolinate (80), the 1,2,3,5,6,7,8,9a-octahydropyrrolo[1,2-a]indoles were obtained.

Chart 13



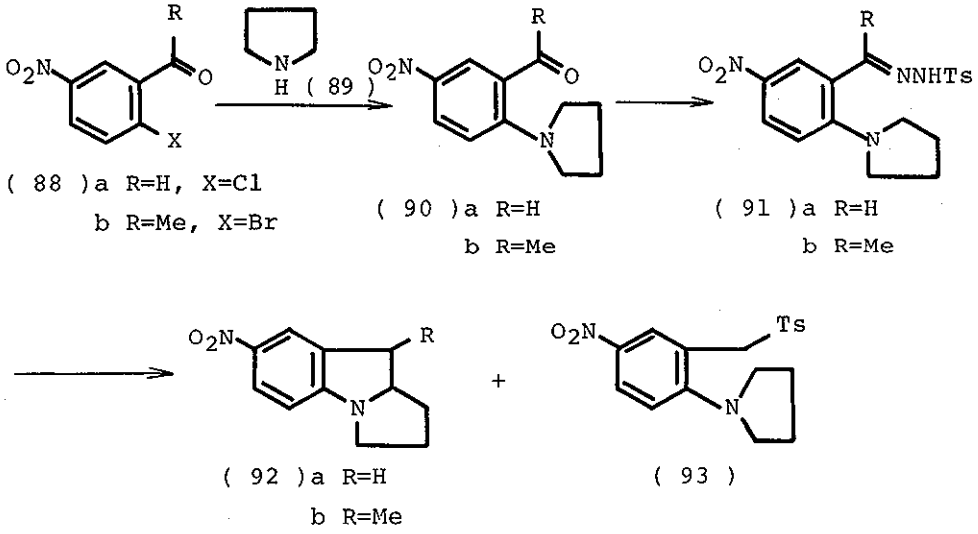
Raines and co-workers[19] reported a convenient route to 9-amino-9H-pyrrolo[1,2-a]indoles via N-(o-carbomethoxyphenyl)pyrrole (28) by the McFadyen-Stevens reaction. Compound 82 was converted directly to 83 by a Mannich reaction. The trimethylammonium iodide (86) was prepared from 84. Catalytic reduction of the dimethylamino compound either as the free base (84) or the hydrochloride salt (83a) was accompanied by prototropic tautomerism to give the known indole 85. Treatment of the quaternary ammonium compound 86 with potassium cyanide gave 9-cyano-3H-pyrrolo[1,2-a]-indole (87).

Chart 14



Garner obtained indolines by treatment of benzaldehyde tosylhydrazones ortho-substituted by tertiary amine with sodium methoxide in diglyme[20]. This method was applied by Takada[21] to the synthesis of 2,3,9,9a-tetrahydro-7-nitro-1H-pyrrolo[1,2-a]indole (92). Condensation of 2-chloro-5-nitrobenzaldehyde (88a) and pyrrolidine (89) gave 5-nitro-2-(1-pyrrolidino)benzaldehyde (90a), whose tosylhydrazone 91a was treated as described above to give in poor yield the objective compound 92a, while the main product was the sulfone 93. On the other hand, the 9-methyl derivative 92b was synthesized in good yield by this method via the tosylhydrazone of 5-nitro-2-(1-pyrrolidino)acetophenone (91b).

Chart 15



(88)a R=H, X=Cl
b R=Me, X=Br

(90)a R=H
b R=Me

(91)a R=H
b R=Me

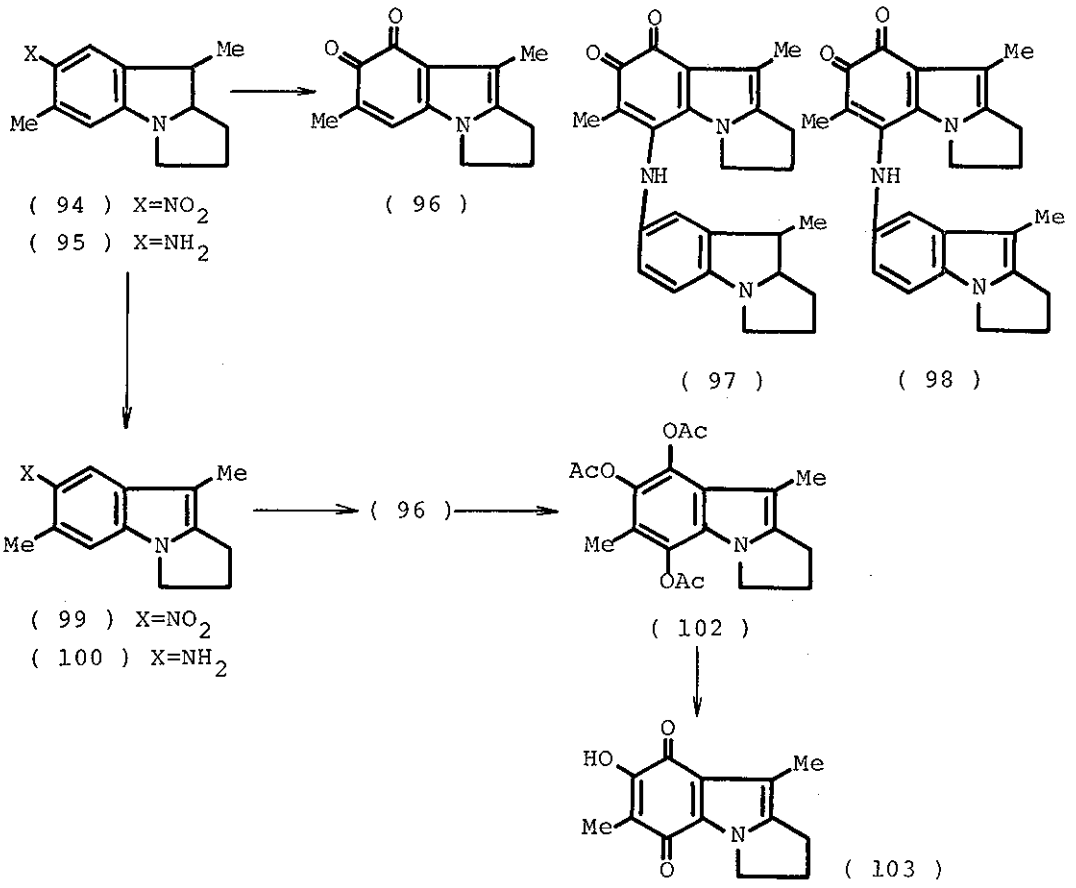
(92)a R=H
b R=Me

(93)

Catalytic reduction of 94, prepared in a similar manner, over Raney nickel in ethanol gave 7-amino-2,3,9,9a-tetrahydro-6,9-dimethyl-1H-pyrrolo[1,2-a]indole (95). Oxidation of 95 with Fremy's

salt afforded a mixture of 96,97 and 98 in low yields. Compound 94 was dehydrogenated with activated manganese dioxide to give 99, which was hydrogenated to 100 followed by Fremy's oxidation to afford the o-quinone 96. Thiele acetoxylation of 96 gave the triacetoxy compound 102, which was hydrolyzed to give 103.[22]

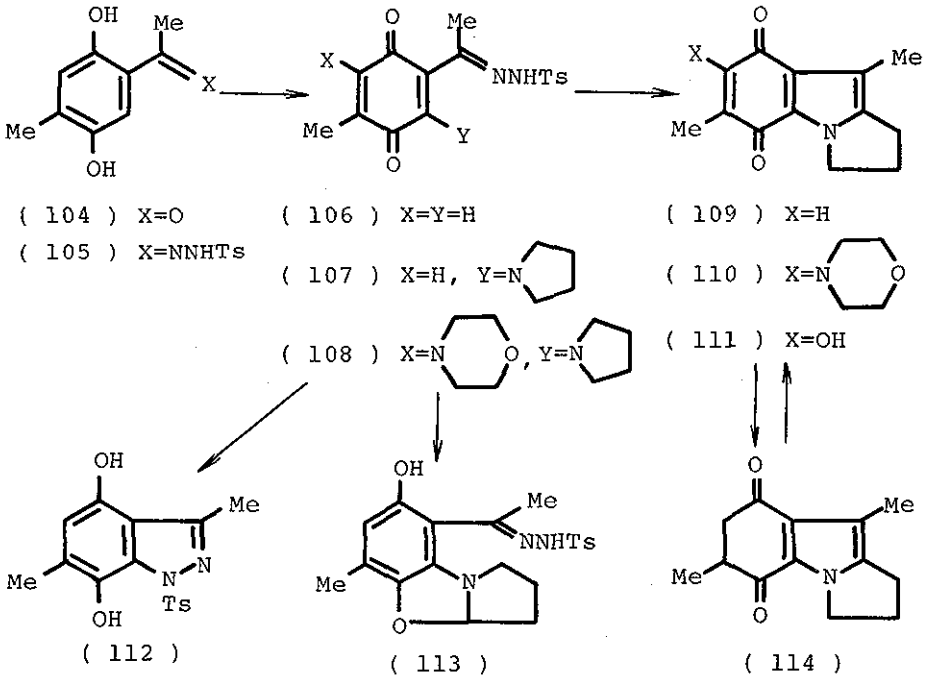
Chart 16



Takada and co-workers also developed a direct synthesis of pyrroloindoloquinones.[23] 2-Acetyl-5-methylhydroquinone tosylhydrazone (105) was oxidized with Fremy's salt affording 2-acetyl-5-methyl-1,4-benzoquinone tosylhydrazone (106) which was treated

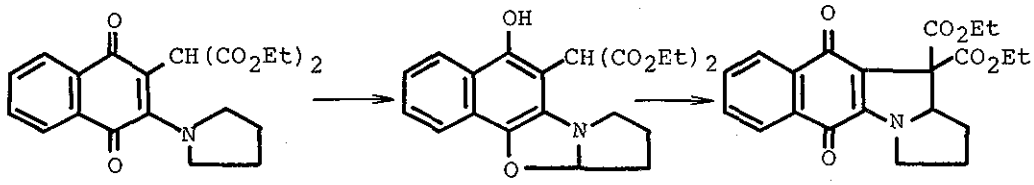
with pyrrolidine to give 2-acetyl-3-(1-pyrrolidino)-5-methyl-1,4-benzoquinone tosylhydrazone (107), followed by thermolysis to furnish 2,3-dihydro-6,9-dimethyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole (109) along with 2,3-dimethyl-1-tosyl-1H-indazole (112). Recently, they obtained on thermolysis or photolysis of 107 a mixture of 109 and 114. This indicated that 113 was a possible intermediate. On refluxing in dimethylformamide 114 was converted into 109, and reduction of 109 with sodium hydrosulfite afforded 114. Furthermore, thermolysis of 2-acetyl-3,6-diamino-5-methyl-1,4-benzoquinone tosylhydrazone (108), afforded the 7-morpholino-(110) and the 7-hydroxypyrrolo[1,2-a]indoloquinone (111). The hydroxy compound 111 was also produced by acid hydrolysis of 110.[24]

Chart 17



In connection with this work, Takada and co-workers[25] reported that photolysis of 2-bis-ethoxycarbonylmethyl-3-(1-pyrrolidino)-1,4-naphthoquinone (115) gave 11,11-bis-ethoxycarbonyl-1,2,5,10,11,11a-hexahydro-5,10-dioxo-3H-pyrrolo[1,2-a]benzo[f]indole (117) via the oxazoline intermediate 116, structurally similar to 113.

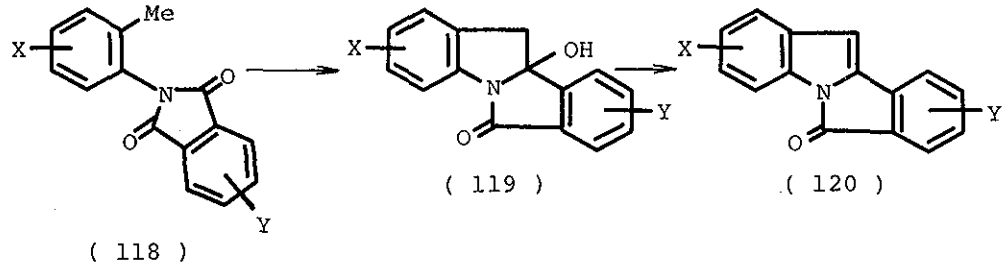
Chart 18



(115) (116) (117)

Based on a study of the photochemistry of the phthalimide system, Kanaoka and collaborators[26] reported the formation of isoindolo-[2,1-a]indol-6-one derivatives 119 on irradiation of N-(2-alkylphenyl)phthalimides 118 with a high pressure mercury lamp in ethanol. The hydroxy compound 119 was dehydrated upon acid treatment to give 120. However, phthalimides with electron-donating groups ($X=NH_2$, NMe_2, and OMe) resisted cyclization.

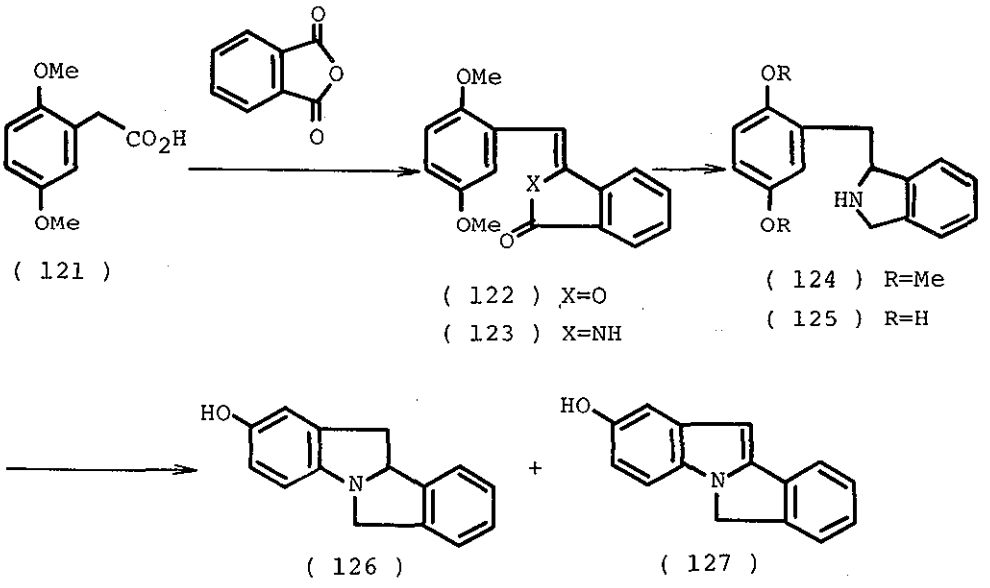
Chart 19



(118) (119) (120)

Takada and Ohki synthesized 6H-isoindolo[2,1-a]indole derivatives, a system related to pyrrolo[1,2-a]indoles.[27] 2,5-Dimethoxyphenylacetic acid (121) was heated with an equimolar mixture of phthalic anhydride and sodium acetate to afford 2,5-dimethoxybenzalphthalide (122) which, in turn, was heated with an excess of formamide to form 3-(2,5-dimethoxybenzal)phthalimidine (123). Compound 123 was electrolytically reduced to 1-(2,5-dimethoxybenzyl)isoindoline (124) which was O-demethylated with 48 % hydrobromic acid to 125 followed by treatment with alkaline potassium ferricyanide to afford 10b,11-dihydro-2-hydroxy-6H-isoindolo[2,1-a]indole (126) and 2-hydroxy-6H-isoindolo[2,1-a]indole (127).

Chart 20



(121)

(122) X=O
(123) X=NH

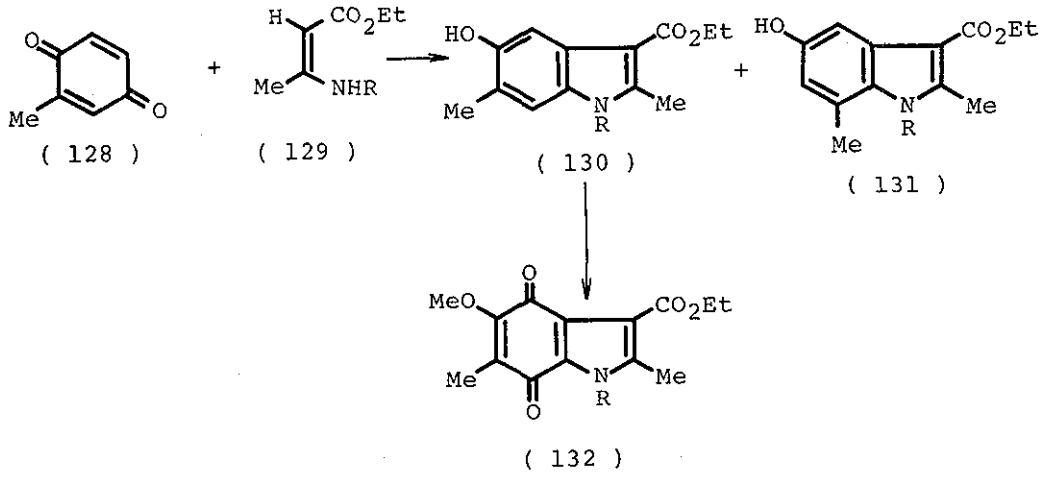
(124) R=Me
(125) R=H

(126)

(127)

The Nenitzescu reaction of toluquinone 128 with 3-alkylamino-crotonates 129 was investigated extensively to define the minimum structural requirements for antibacterial action in the indoloquinone series 132.[28]

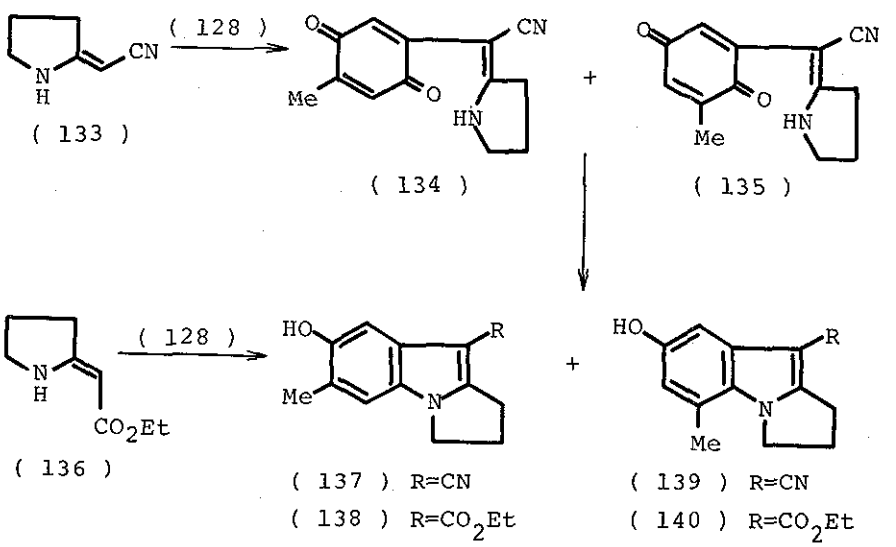
Chart 21



Yamada and Matsui synthesized the 2,3-dihydro-1H-pyrrolo[1,2-a]-indole ring system by condensation of toluquinone 128 and 2-cyanomethylenepyrrolidine 133.[29] When the nitrile 133 was reacted with two equivalents of 128 in the presence of acetic acid, two quinone isomers 134 and 135 were formed in the ratio of 1.6:1. These quinones were separated by silica gel column chromatography and converted in rather poor yield to 9-cyano-2,3-dihydro-7-hydroxy-6-methyl-1H-pyrrolo[1,2-a]indole (137) and 9-cyano-2,3-dihydro-7-hydroxy-5-methyl-1H-pyrrolo[1,2-a]indole (139), respectively, by treatment with aluminum amalgam in the presence of water,

with sodium borohydride in absolute ethanol, or metallic lithium in liquid ammonia. Subsequently, they reported a one-step synthesis of the pyrrolo[1,2-a]indole from toluquinone and 2-carboethoxymethylenepyrrolidine 136 by the Nenitzescu reaction.[30] When two equivalents of toluquinone and one equivalent of the ester 136 were mixed in methanol in the presence of acetic acid at room temperature, 138 and 140 were obtained in the ratio of 1:3.

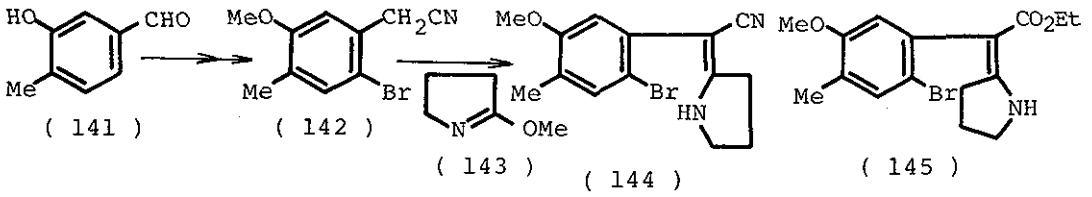
Chart 22



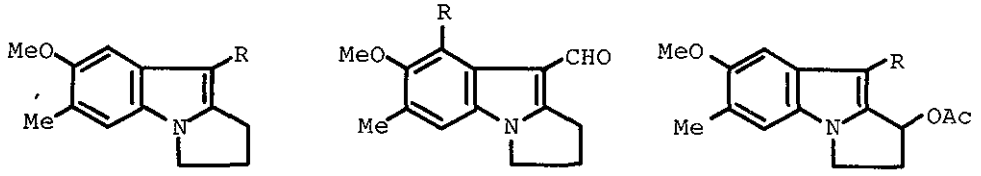
Kametani and collaborators reported a facile synthesis of 2,3-dihydro-1H-pyrrolo[1,2-a]indoles by a route involving an intramolecular nucleophilic aromatic substitution.[31] Condensation of 2-methoxy-Δ^1-pyrroline 143 with 2-bromo-5-methoxy-4-methylphenylacetonitrile (142), readily available from 5-hydroxy-4-methylbenzaldehyde (141), in the presence of 1,5-diazabicyclo-

[5.4.0]undec-5-ene gave α-(2-bromo-5-methoxy-4-methylphenyl)-α-pyrrolidin-2-ylideneacetonitrile (144). (Z)-α-Aryl-α-pyrrolidin-2-ylideneacetate (145) was prepared by ethanolysis of the nitrile 144. Treatment of 144 and 145 with sodium hydride and cuprous bromide in dimethylformamide gave quantitatively the 2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbonitrile (146) and the corresponding ester 147, respectively. Heating the nitrile 146 with nickel-aluminum alloy in aqueous acetic acid yielded the aldehyde 148. The aldehyde was further converted via the 8-nitro compound 150 into the 5,8-quinone 155 which can be converted to 7-methoxymitosene (156) by Weiss' method.[35] On treatment with lead tetraacetate in acetic acid, the pyrroloindoles 146 - 149 were selectively acetylated at the C_1 position to give the acetates 152 - 154.[32] The acetate 153 was converted to 1-acetoxy-7-methoxymitosene (157) and desammono-apomitomycin A (6) by Remers' method.[38] When the acetoxy derivatives were heated in acetic acid, the 3H-pyrrolo[1,2-a]indoles 158 and 159, potential precursors of aziridinopyrrolo[1,2-a]indoles, were obtained.

Chart 23



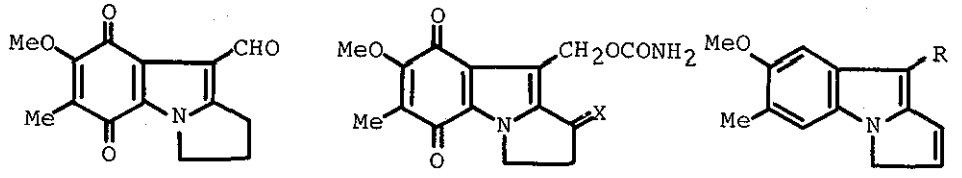
(141) (142) (143) (144) (145)



(146) R=CN
(147) R=CO_2Et
(148) R=CHO
(149) R=CO_2Me

(150) R=NO_2
(151) R=NH_2

(152) R=CN
(153) R=CHO
(154) R=CO_2Me



(155)

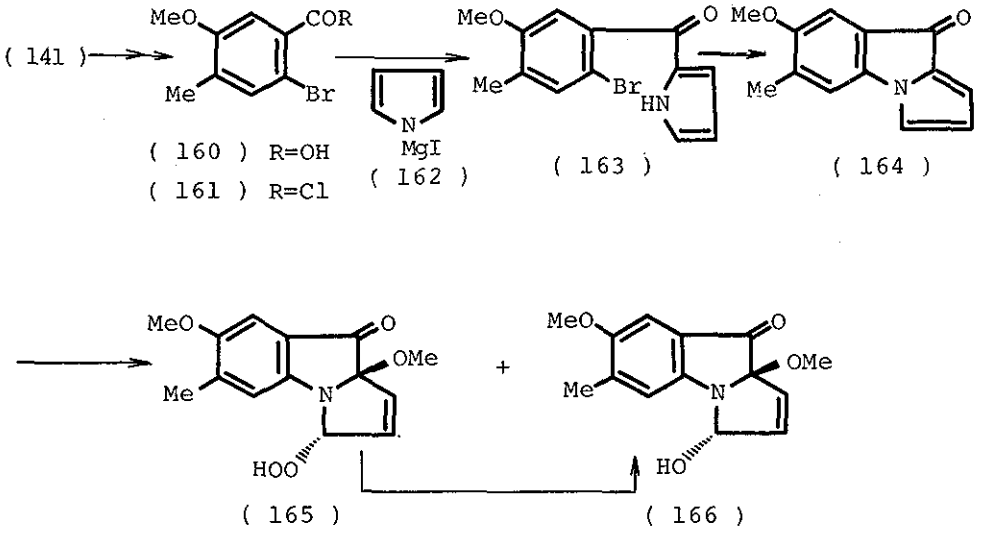
(156) X=H_2
(157) X=H, OAc
(6) X=O

(158) R=CN
(159) R=CO_2Me

Furthermore, Kametani and co-workers synthesized 9-keto-9H-pyrrolo[1,2-a]indole (164) from the above starting material 141.[33] 2-Bromo-5-methoxy-4-methylbenzoic acid (160), easily prepared from 141, was chlorinated with thionyl chloride to afford the acid chloride 161 and condensed with pyrrylmagnesium iodide (162) to afford 2-(2-bromo-5-methoxy-4-methylbenzoyl)pyrrole (163). By a route involving an intramolecular nucleophilic aromatic substitution, 163 was cyclized to provide 164. The introduction of the oxo-

substituent at the C_{9a} position seems to be one of the most difficult problems in the synthesis of the mitomycins. For this purpose, photooxygenation of 9-keto-7-methoxy-6-methyl-9H-pyrrolo-[1,2-a]indole (164) was studied and afforded the desired 9a-oxo-substituted compounds 165 and 166. Though Franck[12] reported that photooxygenation of 38 gave only the dehydrated product, irradiation of 164 in methanol under an oxygen atmosphere in the presence of Rose Bengal as sensitizer with a 200 W tungusten lamp or a halogen lamp gave the two products 165 and 166. The hydroperoxide 165 gave 166 on treatment with dimethyl sulfide or further irradiation in methanol under the same conditions.

Chart 24



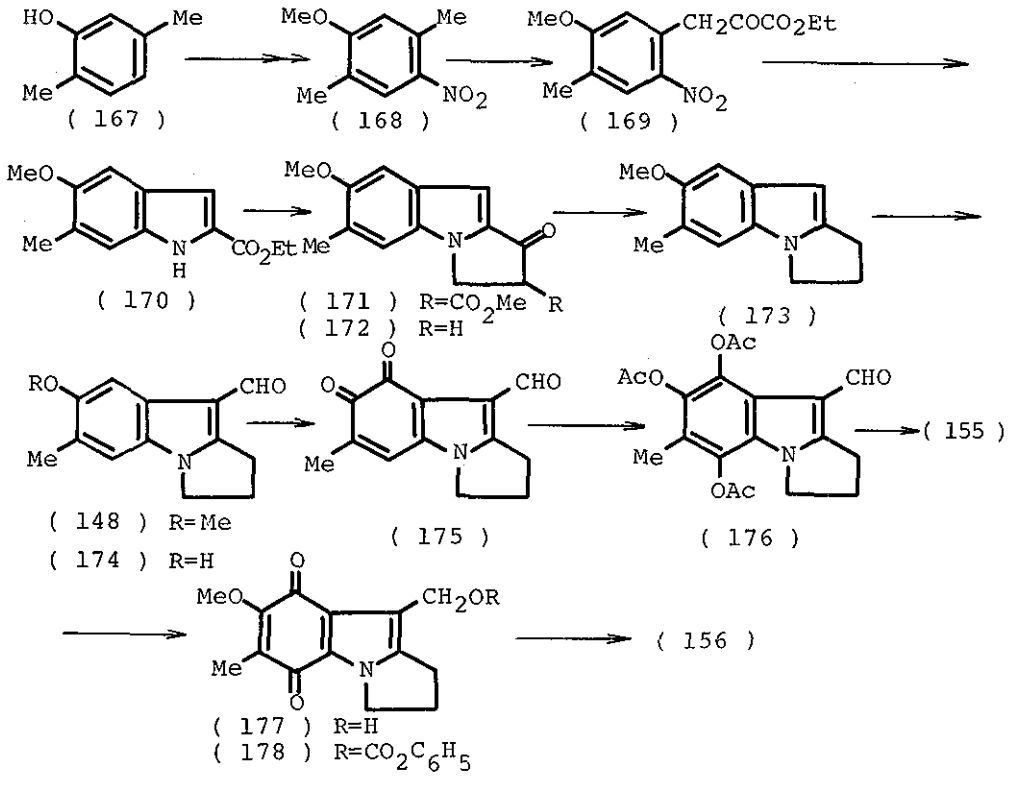
METHOD C

The third method, in which C ring closure occurs, involves bond formation between the C_1-C_{9a}, C_1-C_2, C_2-C_3 or C_3-N linkages. In some cases, more than two bondings take place. One-step ring formation for both B and C rings are also discussed in this section.

Synthetic approaches towards mitomycins and their analogs have been studied energetically by the Lederle group and a large number of pyrrolo[1,2-a]indoles and simpler indoloquinones were synthesized.[34] Their synthesis of the pyrroloindoles involves a base-catalysed 1,4-addition of ethyl indole-2-carboxylate 170 to an acrylic derivative followed by Dieckmann condensation.[35] The appropriately substituted indole 170 was synthesized as follows: 2,5-xylenol (167) was nitrated in three-steps to give 4-nitro-2,5-xylenol (168) which was condensed with ethyl oxalate to afford the phenylpyruvic acid derivative 169. Reductive cyclization of 169 with zinc dust in acetic acid yielded the indole ester 170. On treatment with potassium tert-butoxide and methyl acrylate, the ester 170 furnished 2-carbomethoxy-2,3-dihydro-1-keto-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole (171). Acid-catalysed decarbomethoxylation of 171 gave the tricyclic ketone 172. Wolff-Kishner reduction of 172 gave pyrrolo[1,2-a]indole 173 which was formylated by a Vilsmeyer-Haack reaction to give the aldehyde 148. Cleavage of the methoxy group in 148 gave the phenolic aldehyde 174 which on oxidation with Fremy's salt afforded the o-quinone 175. Thiele acetoxylation of this quinone furnished the triacetate 176, which, on alkaline hydrolysis followed by air oxidation and O-methylation, afforded the 7-methoxy-5,8-pyrrolo[1,2-a]indoloquinone (155).

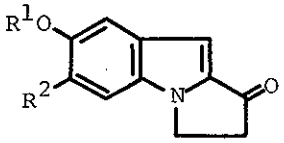
Elaboration of the carbamate side chain from aldehyde 155 was achieved in the following manner. Reduction of 155 with sodium borohydride, followed by oxidation of the intermediate hydroquinone carbinol with acidic ferric chloride, afforded the quinone carbinol 177. Treatment of this carbinol with phenyl chloroformate gave the phenylcarbonate 178 which on ammonolysis was converted into 7-methoxymitosene (156). Compound 156 has all of the structural features of the naturally occurring mitomycins except for an aziridine ring and the element of methanol at the C_9 and C_{9a} position.

Chart 25



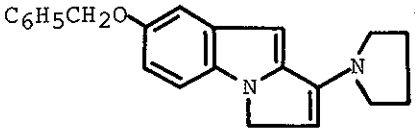
In order to synthesize 1- or 1,2-substituted mitosenes and aziridinomitosenes, Weiss and co-workers examined several reactions of the tricyclic ketones 172a and 172b.[36] Catalytic hydrogenation of the enamine 179 afforded the tertiary amine, the methiodide 180 of which, on treatment with potassium tert-butoxide, furnished the 9H-pyrrolo[1,2-a]indole (181), but not the 3H-pyrrolo[1,2-a]-indole. The 9H-pyrrolo[1,2-a]indole derivatives 182 were also obtained by treatment of the ketone 172 with oxalyl chloride to rearrange the 1H-system into the 9H-system. Thus, the 1-keto group was converted via the 1-chloro group into the 3-oxalyl substituent.[37] Monobromination of the ketone 172 resulted in an attack at the β-indolic carbon to give the 9-bromo derivatives 183. Treatment of the ketone 172 with two equivalents of bromine furnished the 2,9-dibromide 184. Bromination of the enamine 179 gave the 2-bromide 185 which was converted into the 1-acetoxy-2-acetamido-pyrroloindole (188) via the bromo alcohol 186 and the azide 187. The ketone 172b was converted into the oxime 190, oxime tosylate 191, hydrazone 192 and hydrazine 193 by the usual methods, but all attempts to introduce an aziridine group resulted in failure.

Chart 26

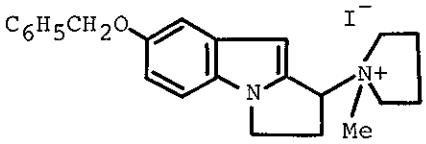


(172)a $R^1=R^2=Me$

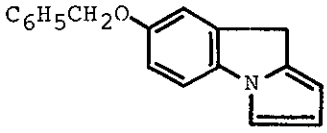
b $R^1=CH_2C_6H_5$, $R^2=H$



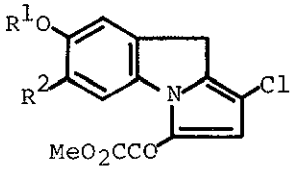
(179)



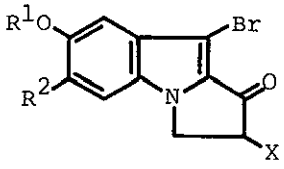
(180)



(181)

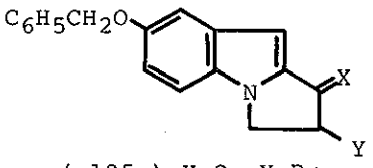


(182)



(183) X=H

(184) X=Br

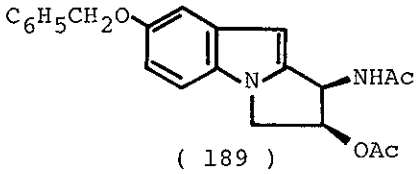


(185) X=O, Y=Br

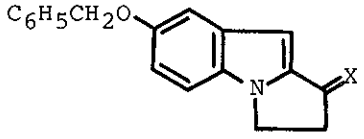
(186) X=H,OH, Y=Br

(187) X=H,OH, $Y=N_3$

(188) X=H,OAc, Y=NHAc



(189)



(190) X=NOH

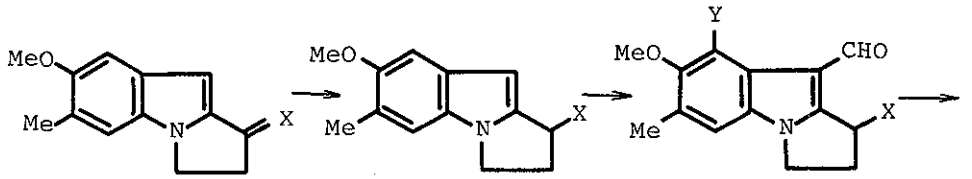
(191) X=NOTs

(192) $X=NNH_2$

(193) $X=H,NHNH_2$

Recently, Remers and colleagues reported the synthesis of 1-substituted[38] and 1,2-disubstituted 7-methoxymitosenes[39] via the results described above. A route to 1-substituted 7-methoxymitosene (157 and 209) was developed from the ketone 172. It involved conversion of the 1-oxo-function into an acetamido or acetoxy group followed by formylation at the C_9 position, quinone-ring elaboration (the shortened sequence of nitration, reduction, and Fremy's oxidation which had not yet been applied to mitosene was used), and conversion of the formyl group into a hydroxymethyl-carbamate. 1-Acetoxymitosene was further transformed into the 1-oxo-analog 6 which was identical with a sample of desammono-apomitomycin obtained by degradation of mitomycin A. This compound 6 not only represents the connection between synthetic and degradative studies of the mitomycins, but is also a versatile intermediate for the preparation of new C-ring analogs.

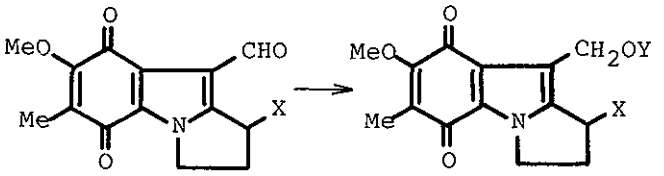
Chart 27



(172) X=O
(194) X=NOH

(195) X=OH
(196) X=OAc
(197) X=NH_2
(198) X=NHAc

(199) X=OAc, Y=H
(200) X=OAc, Y=NO_2
(201) X=NHAc, Y=H
(202) X=NHAc, Y=NO_2

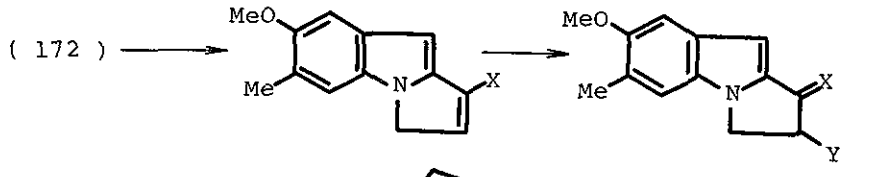


(203) X=OAc
(204) X=NHAc

(205) X=OAc, Y=H
(206) X=OAc, Y=$CO_2C_6H_5$
(157) X=OAc, Y=$CONH_2$
(207) X=NHAc, Y=H
(208) X=NHAc, Y=$CO_2C_6H_5$
(209) X=NHAc, Y=CONHMe
(6) X=O, Y=$CONH_2$

cis-1-Acetamido-2-acetoxy-7-methoxy-N-methylmitosene (221) was prepared in eleven-steps from 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole (172) by a route involving bromination of the pyrrolidine-enamine 210 or the trimethylsilyl enol ether (211) followed by conversion of the bromide 212 via the acetate 213 into the oxime 214. Then elaboration of the quinone and methyl carbamate functions, according to previously established methods, was carried out.

Chart 28



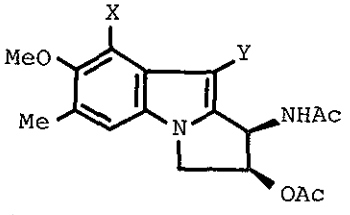
(210) X=N

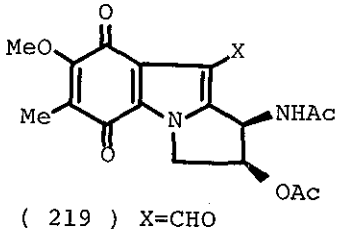
(211) X=OSiMe$_3$

(212) X=O, Y=Br

(213) X=O, Y=OAc

(214) X=NOH, Y=OAc





(215) X=Y=H

(216) X=H, Y=CHO

(217) X=NO_2, Y=CHO

(218) X=NH_2, Y=CHO

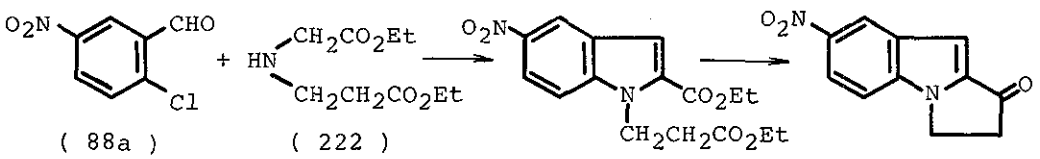
(219) X=CHO

(220) X=CH_2OH

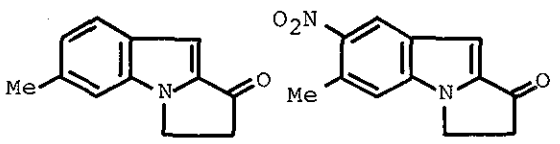
(221) X=$CH_2OCONHMe$

Although 226 could not be obtained by the nitration of 225,[40] 1-keto-7-nitropyrroloindole (224) was synthesized by Takada[21] as follows; N-ethoxycarbonylmethyl-β-aminopropionate (222) was heated with 88a in dimethylformamide in the presence of triethylamine where upon condensation-cyclization proceeded in one-step to give ethyl 1-(2-ethoxycarbonylethyl)-5-nitroindole-2-carboxylate (223). Dieckmann reaction of 223 afforded 2,3-dihydro-1-keto-7-nitro-1H-pyrrolo[1,2-a]indole (224).

Chart 29



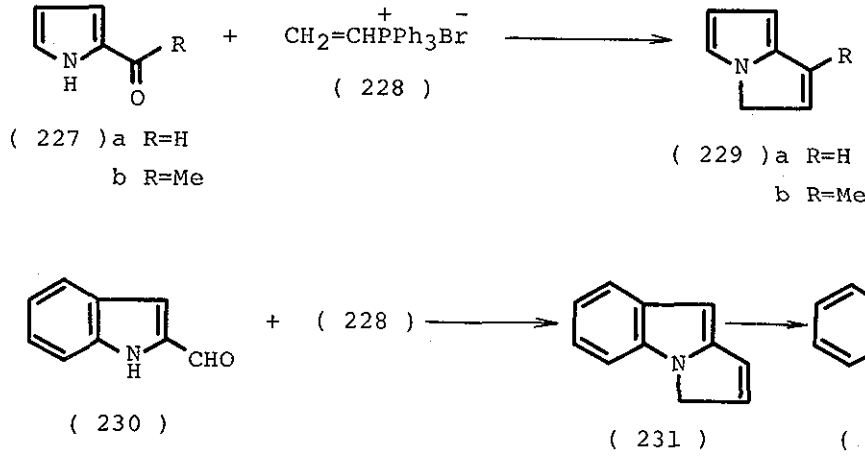
(88a) (222) (223) (224)



(225) (226)

Schweizer and Light found that 2-formyl- or 2-acetylpyrroles reacted with vinyltriphenylphosphonium bromide (228) to form 3H-pyrrolizine (229).[41] They also reported the synthesis of 3H-pyrrolo[1,2-a]indole using this reagent.[42] When indole-2-carboxaldehyde 230 was reacted with 228 in the presence of sodium hydride, 3H-pyrrolo[1,2-a]indole 231 was obtained. Hydrogenation of 231 over rhodium in ethanol gave only partially reduced 2,3-dihydro-1H-pyrrolo[1,2-a]indole 232.

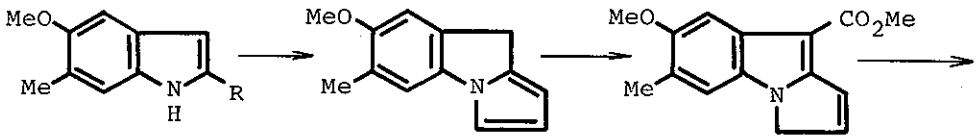
Chart 30



Matsui and co-workers utilized this method to synthesize 1,2-aziridinopyrrolo[1,2-a]indole 240,[43] which has the full ring system of mitomycins, although the chemical shift of the methine proton at C_2 position does not agree with the data reported by Franck.[12] The ester 170 was reduced with lithium aluminum hydride to the alcohol 233, whose oxidation with chromic anhydride-pyridine complex afforded the aldehyde (234). On reaction of 228 in tetrahydrofuran with the aldehyde (234) in the presence of sodium hydride 9H-pyrrolo[1,2-a]indole 235 was obtained. Treatment of 235 with potassium tert-butoxide and dimethyl carbonate afforded the key intermediate, 3H-pyrrolo[1,2-a]indole 159. Functionalization of the vinylic double bond of 159 for attachment of aziridine moiety was achieved by iodine-azide addition giving the iodo-azide (236). Catalytic hydrogenation of 236 in methanol containing hydrogen chloride gave the iodo-amine hydrochloride 237, which upon rapid treatment with alkali afforded the free base. The

amino group of 237 was protected by treatment with methyl chloroformate to furnish the iodo-carbamate (238). The step for cyclization to the aziridine was done with sodium methoxide. However, the tetracyclic system obtained proved not to have an aziridine ring but an oxazoline ring. Revised synthesis of the aziridino-pyrrolo[1,2-a]indole was as follows. Cyclization of the iodo-amine or its hydrochloride 237 with sodium methoxide in boiling methanol afforded a crystalline mixture which was treated with methyl chloroformate and triethylamine to give a mixture of N-methoxycarbonylaziridino-pyrrolo[1,2-a]indole (240), and compounds 241 and 242. The latter presumably formed by ring opening of the aziridine by nucleophilic attack of methoxide anion and protection of the resulting amino group by methyl chloroformate. The aziridine 240 is not so stable and changed by heating over 150° to the rearranged oxazoline (243). Treatment of the iodo-carbamate (238) with sodium methoxide in dimethoxyethane gave no aziridine but the oxazoline 239.

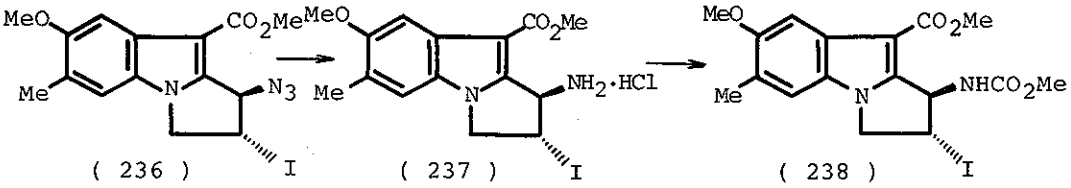
Chart 31



(170) R=CO_2Et
(233) R=CH_2OH
(234) R=CHO

(235)

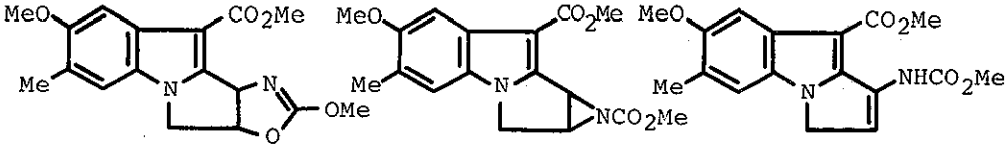
(159)



(236)

(237)

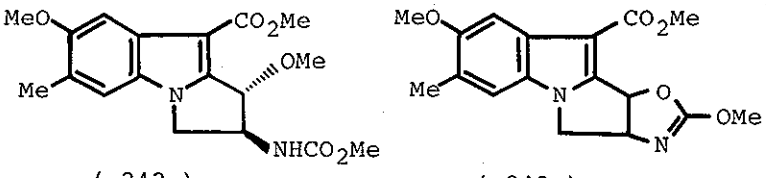
(238)



(239)

(240)

(241)

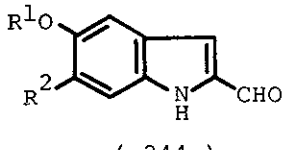


(242)

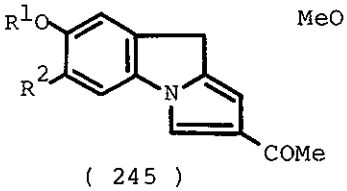
(243)

Furthermore, Matsui and co-workers described a new method for the synthesis of substituted 9H-pyrrolo[1,2-a]indoles 245 and 2,3-dihydro-1H-pyrrolo[1,2-a]indole 247.[44] 5-Alkoxy-2-formylindoles 244 were converted to 2-acetyl-7-alkoxy-9H-pyrrolo[1,2-a]indoles (245) by treatment with methyl vinyl ketone in the presence of trimethylbenzylammonium hydroxide in dioxane. 2-Formyl-7-methoxy-9H-pyrrolo[1,2-a]indole (246) was also obtained by treatment of 244a with acrolein under similar conditions. By reduction of 245 with metallic lithium in liquid ammonia, the 2-acetyl-2,3-dihydro-1H-pyrrolo[1,2-a]indoles (247) were obtained. The methyl ketone 247a was transformed into 2,3-dihydro-2-oximino-1H-pyrrolo[1,2-a]indole (248) by treatment with ethyl nitrite and sodium ethoxide. The oxime of 247 would not undergo Beckmann rearrangement to give 2-acetylaminopyrroloindole. Attempts to prepare the aziridino-pyrroloindole by refluxing the oxime 248 with lithium aluminum hydride in tetrahydrofuran were unsuccessful.

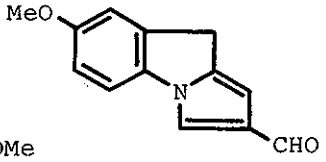
Chart 32



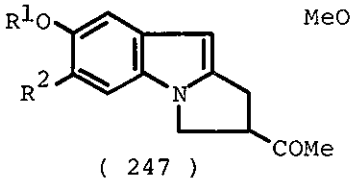
(244)



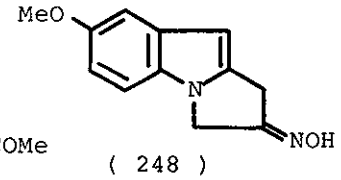
(245)



(246)



(247)

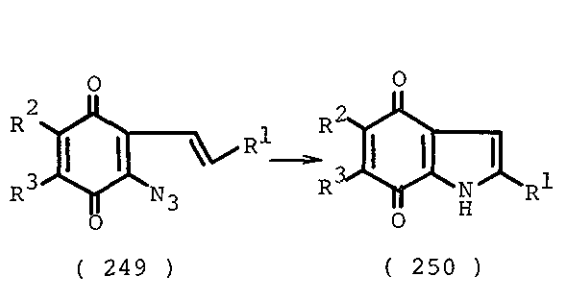


(248)

a R^1=Me, R^2=H
b R^1=$CH_2C_6H_5$, R^2=H
c R^1=$CH_2C_6H_5$, R^2=Me

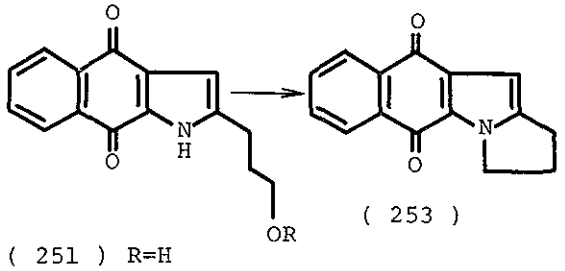
Germeraad and Moore developed a convenient synthesis of indoloquinones.[45] Thermolysis of the 2-azido-3-vinyl-1,4-quinones 249 in refluxing benzene resulted in their transformation to the corresponding indoloquinones 250 in good yield. Hydrolysis of 250e in refluxing aqueous methanolic hydrochloric acid gave the alcohol 251. Treatment of the alcohol with p-toluenesulfonyl chloride in pyridine gave the tosylate 252 which was reacted with potassium tert-butoxide to give 1,2,5,10-tetrahydro-3H-pyrrolo[1,2-a]benzo[f]indole-5,10-dione (253).

Chart 33



(249) (250)

	R^1	R^2	R^3
a	Me		
b	Pr		
c	$(CH_2)_9CH_3$		
d	C_6H_5		
e	$(CH_2)_3OAc$		
f	C_6H_5	Me	Me



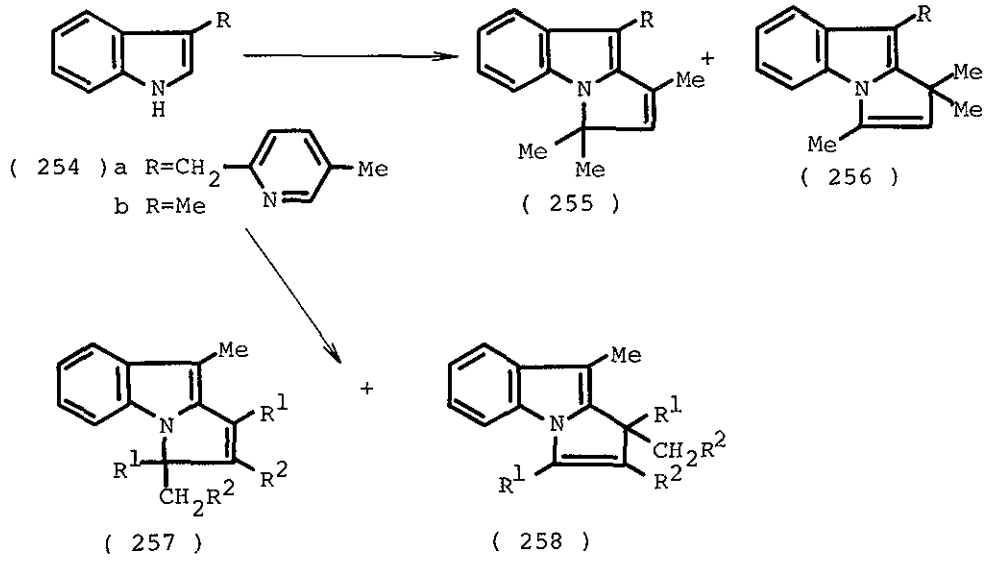
(253)

(251) R=H

(252) R=Ts

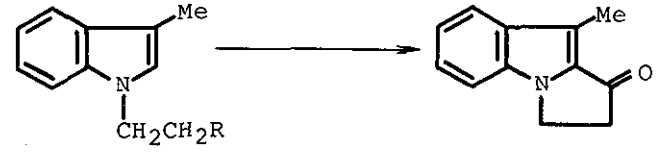
Röder reported several reactions of indole derivatives which would afford pyrrolo[1,2-a]indoles. Condensation of 3-(5-methyl-2-picolyl)indole (254a) with acetone in the presence of aluminum chloride leads to both possible pyrrolo[1,2-a]indoles 255a and 256a. The condensation of 3-methylindole with acetone and aluminum chloride leads, essentially in the ratio of 1:2, to two possible pyrroloindoles 255b and 256b.[46] Moreover, in the presence of carbon disulfide, 3-methylindole reacts with aluminum chloride to form a complex, whose condensation with enolisable ketones such as benzyl methyl ketone and ethyl methyl ketone, leads to the pyrroloindoles 257 and 258.[47]

Chart 34



Condensation also occurs when appropriately substituted indoles are treated with dehydrating agent.[48] The reaction of 3-methylindole with acrylonitrile afforded 1-(β-cyanoethyl)-3-methylindole (259). The nitrile 259 was hydrolysed to the corresponding carboxylic acid 260 which was treated with phosphorus pentoxide to give cyclized compound, 2,3-dihydro-9-methyl-1-oxo-1H-pyrrolo-[1,2-a]indole (261). This result makes a contrast with that of Weiss[35], where indole-1-propionic acid gave no cyclized product. Furthermore, Röder[49] examined the reaction of some 3-substituted indoles with diketene. The product of this reaction, 1-acetoacetylindole 262, was treated with polyphosphoric acid to yield the 3H-pyrrolo[1,2-a]indol-3-one (263).

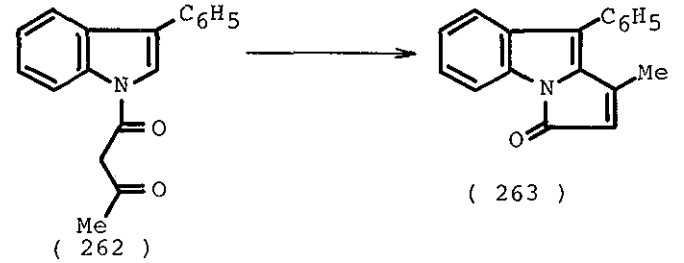
Chart 35



(259) R=CN

(260) R=CO_2H

(261)

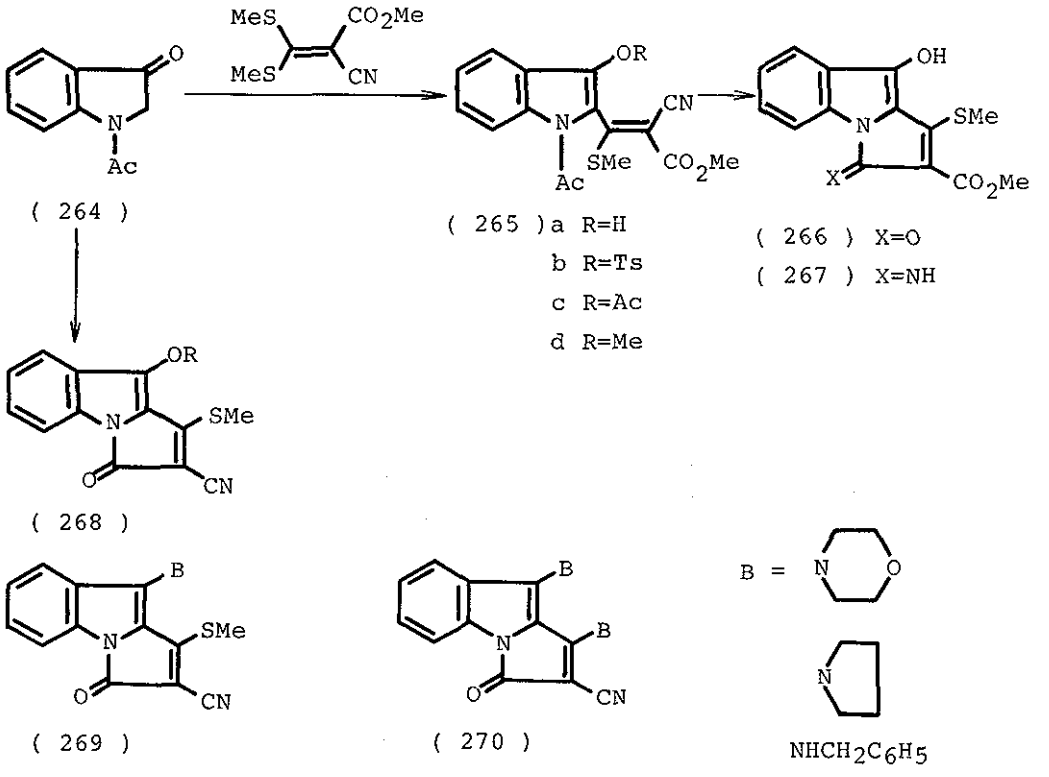


(262)

(263)

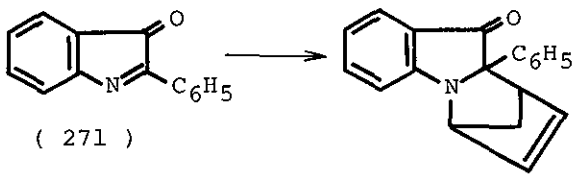
Kobayashi and collaborators synthesized some pyrrolo[1,2-a]-indole in the course of their investigating the reaction of ketenethioacetals.[50] Reaction of 1-acetyl-3-indolinone 264 with methyl 1-cyano-2,2-bismethylthioacrylate in the presence of one equivalent of sodium hydride afforded 1-acetyl-2-(2-cyano-2-methoxycarbonyl-1-methylthiovinyl)-3-hydroxyindole (265a). When an excess of sodium hydride was used, 268 was obtained. Treatment of 265a with hydrochloric acid or hydrogen chloride gas in methanol gave 266 and 267, respectively. Reaction of the tosylate, acetate and methyl ether of 265a with sodium hydride resulted in the formation of the corresponding pyrrolo[1,2-a]indoles 268b-d. Treatment of 268 with amines such as morpholine, pyrrolidine and benzylamine afforded 1-amino- or 1,9-diamino-3H-pyrrolo[1,2-a]indol-3-one derivatives.

Chart 36



The Diels-Alder reaction can be applied to prepare the related ring system.[51] The indolone 271 reacted at room temperature with cyclopentadiene in benzene in the presence of aluminum chloride or perchloric acid to give the Diels-Alder adduct 272.

Chart 37

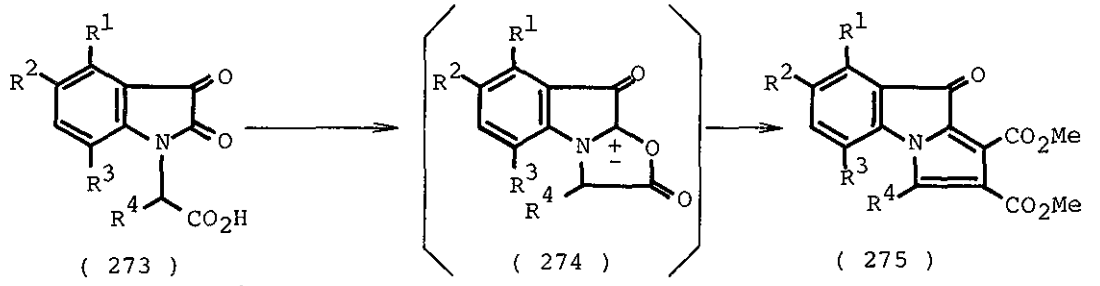


(271)

(272)

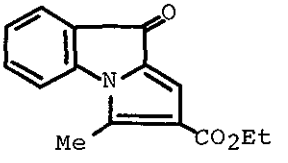
Anderson and Corey reported the synthesis of 9-keto-9H-pyrrolo-[1,2-a]indole using a 1,3-dipolar cycloaddition for the ring C formation.[52] The starting isatin was converted to the sodium salt by treatment with sodium hydride in hexamethylphosphoric triamide, the salt was alkylated with ethyl 2-bromopropionate and without isolation the resulting ester was saponified to give the corresponding isatin-N-(α-methyl)acetic acid (273). When 273 was treated with acetic anhydride, the mesoionic intermediates 274 were formed which underwent 1,3-dipolar cycloaddition reaction in situ with dimethyl acetylenedicarboxylate to give 275. Ethyl propiolate, a less reactive dipolarophile, and 273 gave only 276 with no evidence of the other possible isomer.

Chart 38



(273) (274) (275)

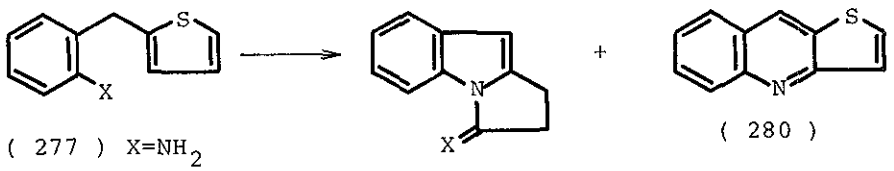
	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	H	H	Me
c	H	Br	H	Me
d	H	Me	H	Me
e	Cl	H	Cl	Me
f	H	Cl	Cl	Me
g	Cl	H	OMe	Me



(276)

Cliff and co-workers found that intramolecular insertion of an intermediate nitrene occurs readily when 2-azidodiphenylmethane is heated.[53] 2-(2-Aminobenzyl)thiophene (277) was prepared from 2-(2-nitrobenzoyl)thiophene by sequential catalytic reduction and Huang-Minlon reduction. Diazotization and treatment with azide ion gave 2-(2-azidobenzyl)thiophene (278) which decomposed in trichlorobenzene at 180° to give 279a, 279b and 280 in a rather poor yield. Since oxygen was not excluded from the work-up, 279b probably arose by oxidation of compound 279a.

Chart 39



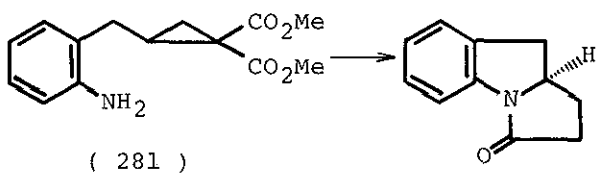
(277) X=NH_2
(278) X=N_3

(279)a X=S
b X=O

(280)

Danishefsky and Doehner reported the synthesis of the mitosane analog 282 by ring mutation of the cyclopropane derivative 281.[54]

Chart 40



(281)

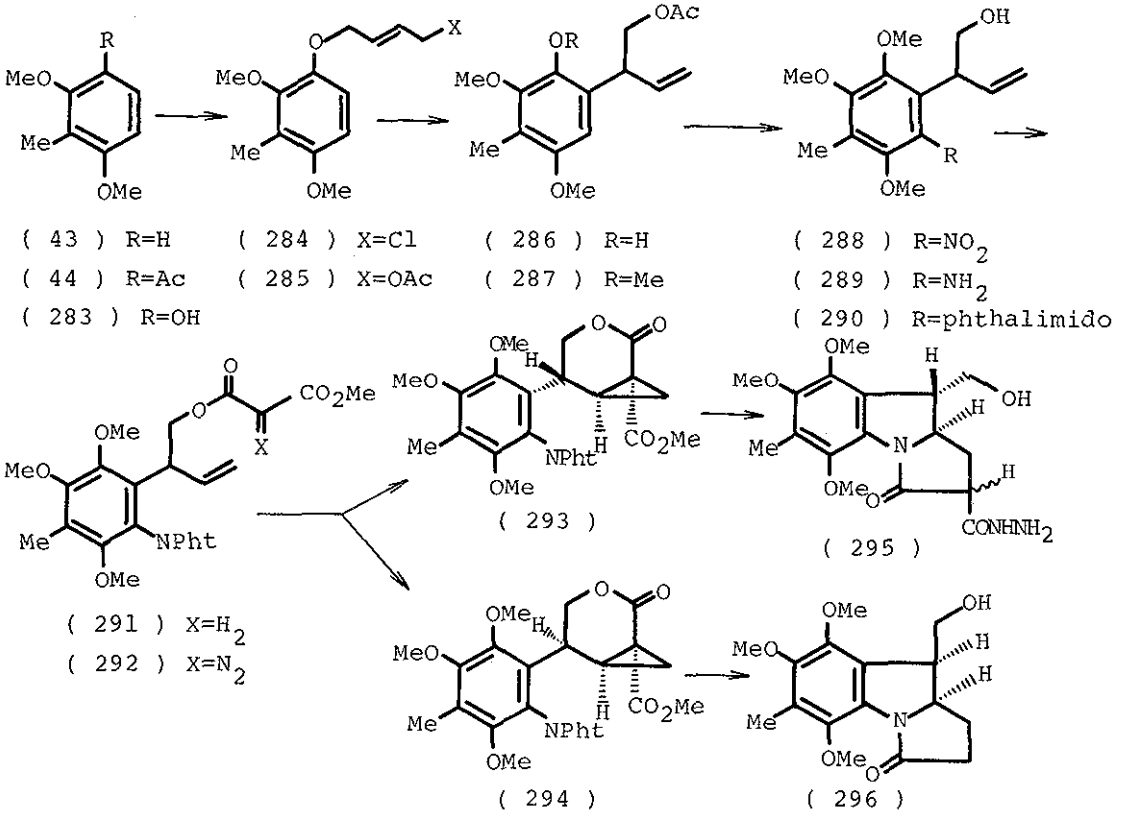
(282)

They also reported the synthesis of the heavily functionalized mitosane analogs 295 and 296 by this method. Friedel-Crafts acetylation of 43 gave 44, which was oxidized by the Baeyer-Villiger method followed by alkaline hydrolysis to give 283. The phenoxide salt was alkylated with trans-1,4-dichloro-2-butene and the resultant 284 was transformed into the acetate 285. Claisen rearrangement afforded 286 which was methylated to give 287. Nitration of 287 followed by hydrolysis of the acetate gave 288. Reduction of 288 with zinc dust in hydrochloric acid afforded 289 which was transformed into the phthaloyl derivative 290 by the action of phthalic anhydride. Acylation with carbomethoxyacetyl

chloride-pyridine gave 291 which was converted with tosyl azide and triethylamine into the mixed diazomalonate 292.

Heating 292 in the presence of copper bronze furnished 293 and 294 in a ratio of 5:1, respectively. The minor cyclopropane 294 was treated with an excess of hydrazine in hot methanol. Thermolysis of the resultant amine-hydrazide gave a lactam-hydrazide which on acidic hydrolysis and decarboxylation afforded the mitosane precursor 296. The major cyclopropane 293 was treated similarly to yield after thermolysis the epimeric lactam-hydrazide 295.

Chart 41

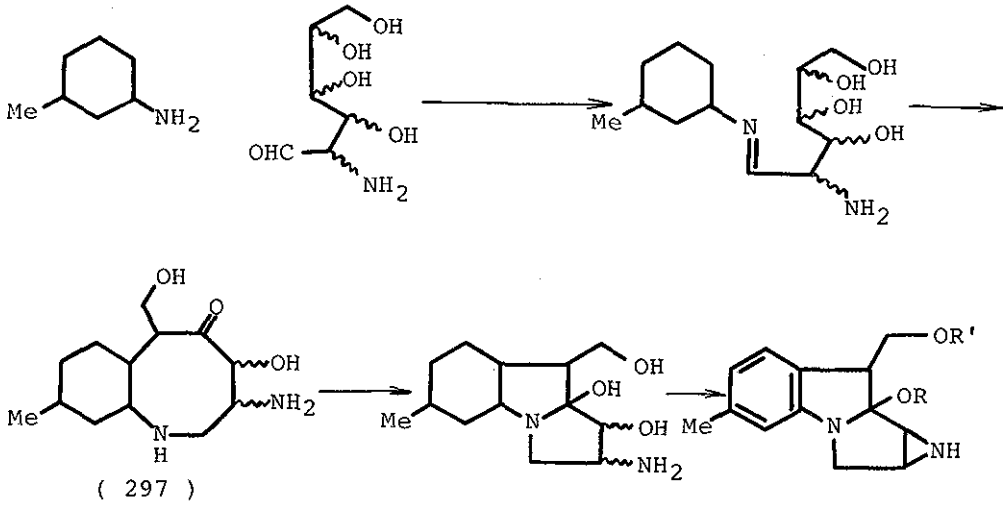


METHOD D

The last method which we discuss in this review is C_{9a}-N bond formation. This method is the most promising approach for the synthesis of 9a-oxo-substituted pyrrolo[1,2-a]indole.

Based on the biosynthetic studies by Hornemann, Lown and co-workers[55] supposed that the appropriately substituted hexahydrobenzazocinone 297 would be a possible intermediate in the synthesis and biosynthesis of mitomycins.

Chart 42

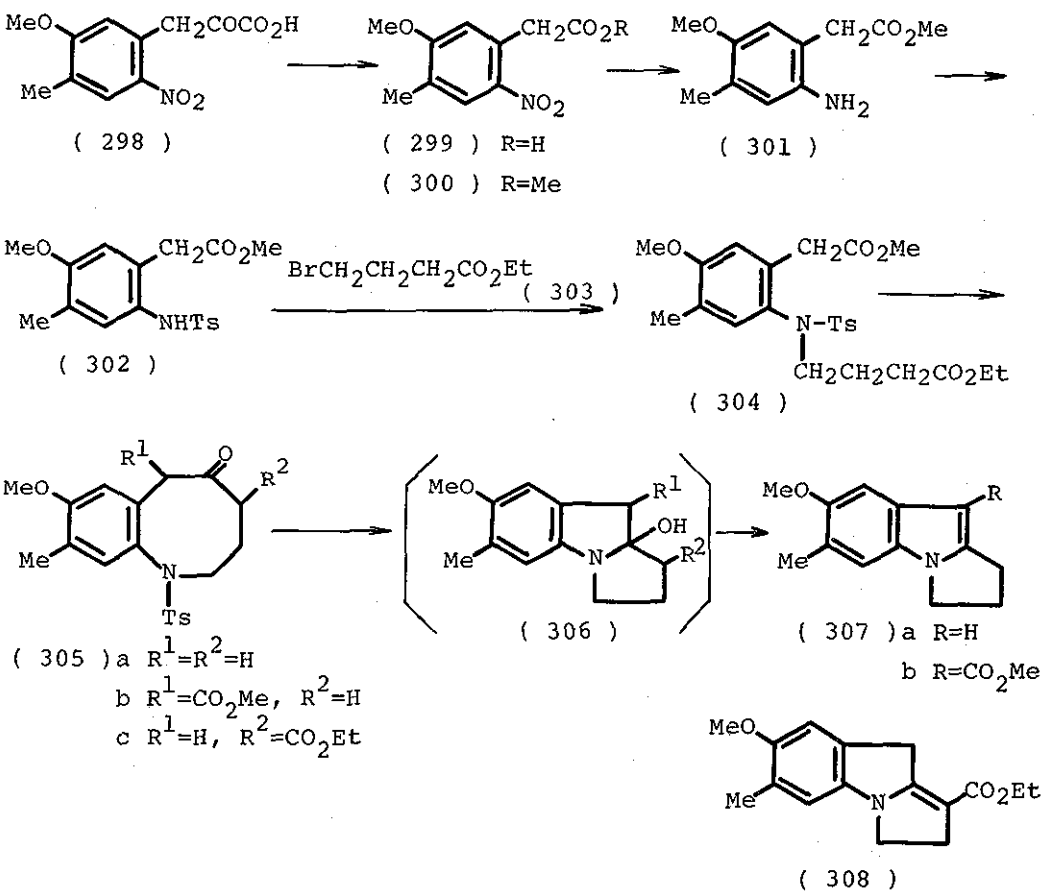


(297)

Thus, they synthesized the eight-membered ring compounds 305 and examined their transannular cyclization of 305 as follows: o-nitrophenylpyruvic acid (298) was oxidatively decarbonylated to o-nitrophenylacetic acid (299). Esterification of the latter followed by catalytic hydrogenation of the nitro group over palladium at atmospheric pressure afforded methyl 2-amino-5-methoxy-4-methyl-

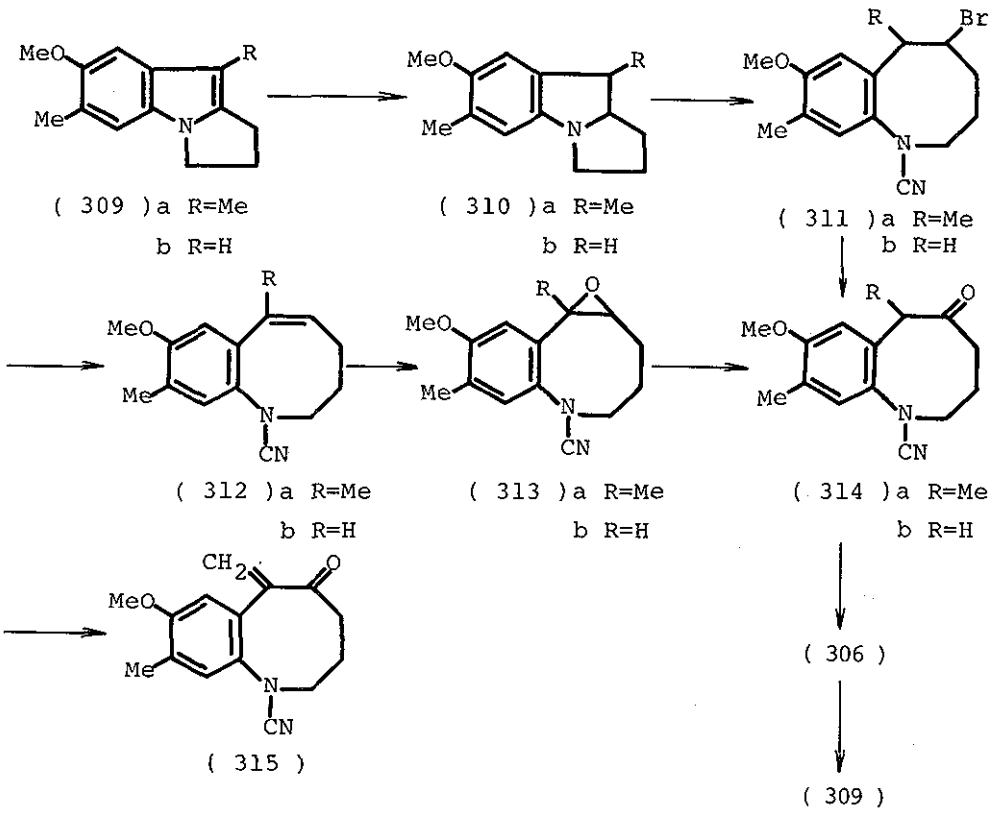
phenylacetate (301). Formation of the N-p-toluenesulfonyl derivative from 301 proceeded smoothly by treatment with p-toluenesulfonyl chloride in pyridine. The benzazocin-5-one 305 was prepared from 302 by alkylation with ethyl γ-bromobutyrate (303) followed by Dieckmann cyclization of the resulting diester 304. Reductive cleavage of the N-S bond was accomplished with sodium in liquid ammonia. However, instead of the desired transannulated product 306, the dehydrated compounds 307 and 308 were produced.

Chart 43



Kametani and collaborators found that 2,3-dihydro-1H-pyrrolo-[1,2-a]indole can be transformed to benzazocin-5-ones, potential intermediates of mitomycins.[56] The starting pyrrolo[1,2-a]indole 309 was reduced to the tetrahydro derivatives 310 with sodium borohydride in acetic acid. Treatment of 310 with cyanogen bromide in benzene cleaved selectively the bond between the carbon at C_{9a} and the nitrogen to furnish the benzazocine derivative 311. Oxidation of 311 was firstly carried out by heating with dimethyl sulfoxide in the presence of sodium hydrogen carbonate, but the objective ketone 314 was obtained in poor yield. Thus, the bromide 311 was converted to 314 in three-steps as follows. Dehydrobromination of 311 by heating with 1,5-diazabicyclo[5.4.0]undec-5-ene in tetrahydrofuran yielded the olefin (312) which was treated with m-chloroperbenzoic acid in methylene chloride to give the epoxide 313. Treatment of 313 with boron trifluoride etherate in benzene at room temperature provided the target ketone 314. Reaction of the ketone (314b) with formaldehyde in the presence of sodium hydride gave the methylene compound (315) while treatment with ethanolic sulfuric acid gave a quantitative yield of the pyrrolo-[1,2-a]indoles 309.

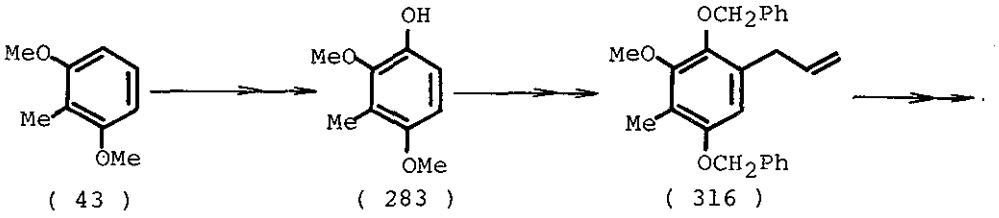
Chart 44



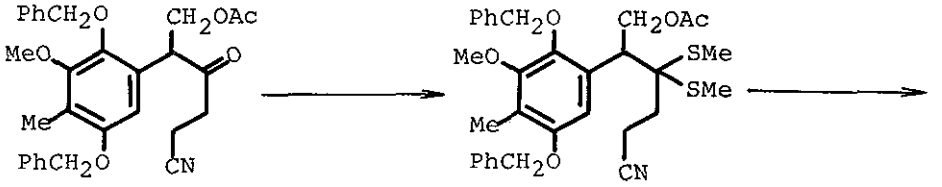
More recently, Kishi and co-workers reported a total synthesis of deiminomitomycin A (325)[57]. This synthesis involves two key cyclizations; the intramolecular Michael reaction to construct the eight-membered ring (321) and the transannular cuclization of 323 to 324 under conditions mild enough to introduce and preserve the 9a-methoxy group. The nitrile 317 was synthesized in 13 steps from 2,3-dimethoxy-3-methylphenol (283) readily available from 2,6-dimethoxytoluene 43. Lithium aluminum hydride reduction of the nitrile 318 in ether gave the amine 319 which was subjected to

hydrogenolysis followed by treatment with oxygen to afford the eight-membered quinone 321. Phenyl chloroformate treatment of 321 in methylene chloride containing pyridine gave the phenyl carbonate 322. Careful treatment of 322 with methanethiol containing a catalytic amount of boron trichloride etherate afforded the hemithioketal 323. The crucial transannular cyclization of 323 was effected by mercuric chloride in methylene chloride containing a small amount of triethylamine. The product was isolated as an about 1:1 mixture of cis-trans isomers. Upon contact with weak acid such as a catalytic amount of acetic acid in methylene chloride or thin layer chromatography on silica gel, 324 was smoothly and quantitatively converted to the indoloquinone 178. Brief ammonia treatment of 324 gave deiminomitomycin A (325) as about 1:1 mixture of cis-trans isomers. During attempted separation of the isomers by preparative thin layer chromatography on alumina, most of the cis-isomer decomposed to the known indoloquinone 156 while the bulk of the trans-isomer remained intact. Deiminomitomycin A could be quantitatively converted to 7-methoxymitosene (156) under such weakly acidic conditions as a catalytic amount of acetic acid in methylene chloride or even thin layer chromatography on silica gel. It is interesting to note that deiminomitomycin A is much less stable than the naturally occurring mitomycins.

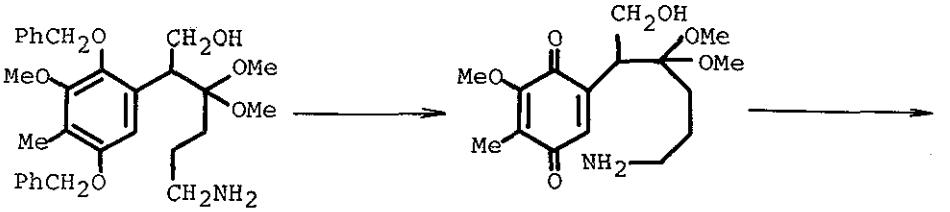
Chart 45



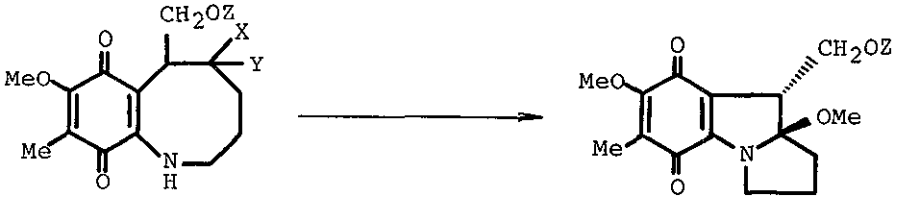
(43) (283) (316)



(317) (318)



(319) (320)



(321) X=Y=OMe, Z=H
(322) X=Y=OMe, Z=CO_2Ph
(323) X=OMe, Y=SMe, Z=CO_2Ph

(324) Z=CO_2Ph
(325) Z=$CONH_2$

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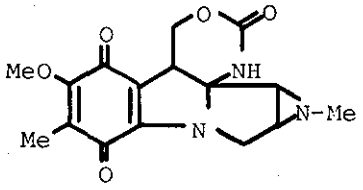
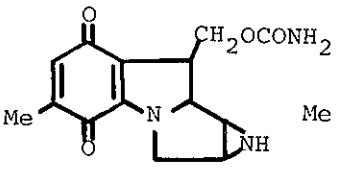
1 a) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, J. Amer. Chem. Soc., 1962, 84, 3185; idem, ibid., 1962, 84, 3187.

b) For the X-ray crystallographic study: A. Tulinsky, J. Amer. Chem. Soc., 1962, 84, 3188; R. Yahashi and I. Matsubara, J. Antibiotics (Tokyo), 1976, 29, 104.

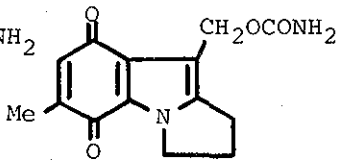
c) For the structure determination of related compound mitiromycin (i): G. O. Morton, G. E. Van Lear, W. Fulmor, J. Amer. Chem. Soc., 1970, 92, 2588.



(i) mitiromycin



(ii) mitosane



(iii) mitosene

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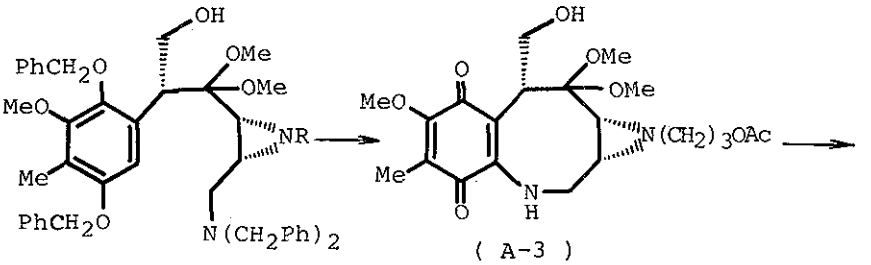
Addendum

After our original manuscript had been submitted in this Journal, the following significant synthetic developments in the pyrrolo[1,2-a]indole field appeared in the literature.

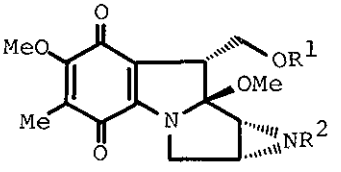
Kishi and his collaborators have recently reported the total syntheses of porfiromycin (A-8)[58a], mitomycin A (A-6) and C (A-7).[58b] Dibenzylamine aziridine (A-1) was converted to 3-acetoxypropyl-aziridine (A-2). Hydrogenolysis of A-2, followed by treatment with oxygen, yielded the eight-membered quinone (A-3). Careful treatment of A-3 with tetrafluoroboric acid in methylene chloride at room temperature afforded decarbamoyl-N_1-(3-acetoxypropyl)-mitomycin A (A-4), which was converted to N_1-(3-acetoxypropyl)-mitomycin A (A-5). The protecting group of the aziridine moiety of A-5 was removed in three-step to give (±)-mitomycin A (A-6). The transformation of mitomycin A (A-6) to mitomycin C (A-7) and porfiromycin (A-8) has been previously reported.[1]



(A-1) R=H

(A-2) R=$(CH_2)_3OAc$

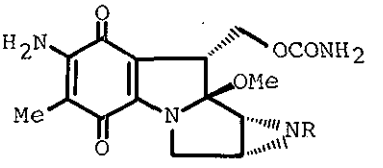
(A-3)



(A-4) R^1=H, R^2=$(CH_2)_3OAc$

(A-5) R^1=$CONH_2$, R^2=$(CH_2)_3OAc$

(A-6) R^1=$CONH_2$, R^2=H
Mitomycin A



(A-7) R=H
Mitomycin C

(A-8) R=Me
Porfiromycin

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