SYNTHETIC STUDIES ON MITOMYCINS AND RELATED COMPOUNDS

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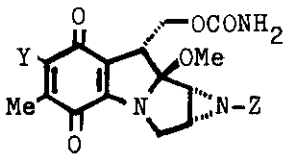
Abstract —— Synthetic approaches towards mitomycins and their analogs are described. The strategy of this study includes a simple synthesis of mitosene derivatives and their transformation to seco-mitosane type compounds which have been shown to be key intermediates in the total synthesis of the mitomycins. Synthetic studies on mitomycins appearing in the literature are also reviewed.

CONTENTS

INTRODUCTION

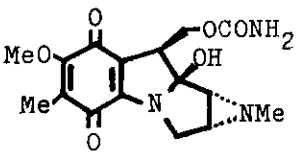
Mitomycin antibiotics were isolated in 1955 by Hata et al.[1] from culutures of Streptomyces caespitosus. These compounds have been found to be active against Ehrlich's cancer cells and Yoshida's sarcoma, as well as against Gram positive and Gram negative bacteria. Hata et al.[2] and Wakaki et al.[3] separated three crystalline compounds named mitomycin A, B and C. Later, Herr et al.[4] isolated porfiromycin from S. ardus, and Lefemine et al.[5] isolated mitiromycin, together with above four antibiotics, from S. verticillatus. In 1962, Webb et al.[6] determined the structures of the mitomycins as follows: Reaction of mitomycin A with methanolic ammonia gave mitomycin C. Similarly, N-methylmitomycin A, made by treatment of mitomycin A with methyl iodide and sodium hydrogen carbonate in dimethylformamide, afforded porfiromycin.[7] Although mitomycin B could not be obtained directly from, or converted to, any of the other antibiotics, it has been degraded, by treatment with 0.1N hydrochloric acid, to a product which has been shown to be identical to that obtained from similar treatment of N-methylmitomycin A. The chromophores of mitomycin A and B were identified by the similarity of their ultraviolet (u.v.) spectra to that of 2-dimethylamino-5-methoxybenzoquinone (7). Likewise

Chart 1

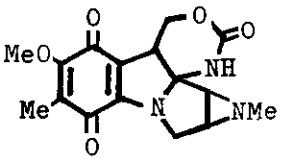


(1-4)

	Y	Z
(1)Mitomycin A	MeO	H
(2)N-Methyl-Mitomycin A	MeO	Me
(3)Mitomycin C	NH_2	H
(4)Porfiromycin	NH_2	Me



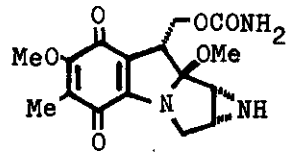
(5)
Mitomycin B



(6)
Mitiromycin

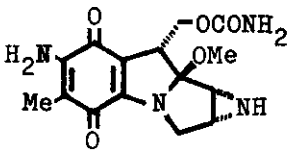
the chromophores of mitomycin C and porfiromycin were similar to that of 2,5-bisdimethylaminobenzoquinone (8). On standing in 0.1N-hydrochloric acid at 25°C for a few hours, mitomycin A underwent a marked change forming one mole of methanol and a new product, named apo-mitomycin A, containing one C-methyl, one O-methyl, one hydroxyl and one amino group. This compound proved to have the $-CH_2OCONH_2$ group from its infrared (i.r.) spectrum, and by its acidic hydrolysis to form carbon dioxide and ammonia. Hydrolysis of apo-mitomycin A (9) in 0.1N-sodium hydroxide liberated one mole of methanol and resulted in a new product (10), whose chromophore was similar to that of 5,6,7,8-tetrahydro-3-hydroxy-2-methyl-1,4-carbazoledione(11). The arrangement of the groups (-OH, $-NH_2$, $-CH_2OCONH_2$) on the skeleton of (9) was established by its treatment with nitrous acid to produce a compound (12), called desammono-apo-mitomycin A, which contained a new carbonyl group, and lacked the NH_2 and OH groups of (9). As the u.v. spectrum of (12) indicated probable conjugation of the new carbonyl function with the indoloquinone chromophore but was unlike that of (13), the new carbonyl was assigned to the 2-position.[8] The nuclear magnetic resonance (n.m.r.) spectrum of (12) displayed two widely separated triplets characteristic of an A_2X_2 system not shown by (9). This suggested the presence of the moiety $N-CH_2-CH_2CO-$ at the 2-position of indole (N atom had to be the indole nitrogen) and (12) must have been formed by a pinacolic deamination of a 1,2-aminoalcohol function in (9). The formation of a 1,2-aminoalcohol[9] from mitomycin A by acid hydrolysis suggested that mitomycin A contained a fused aziridine ring (in the i.r. spectrum of mitomycin A, a weak band at 3030 cm^{-1} is assignable to aziridine C-H stretching). The acid-labile methoxy group could be assigned to the C-9a position as a typical twelve peak ABX pattern was present in the n.m.r. spectrum as expected for the coupling of the single proton on C-9 with the dissimilar protons at C-10. The above considerations lead to the structural formula (1) for mitomycin A. This structure was confirmed by

Chart 2



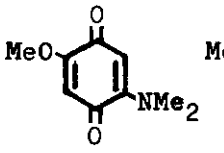
(1) Mitomycin A

$\lambda_{max.}$(MeOH)nm(ε)
218 (17,400)
320 (10,400)
520 (1,400)



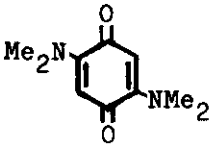
(3) Mitomycin C

$\lambda_{max.}$(MeOH)nm(ε)
217 (24,600)
360 (23,000)
555((209)



(7)

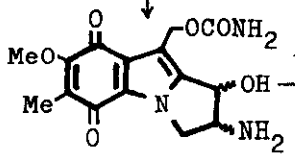
$\lambda_{max.}$(MeOH)nm(ε)
218 (18,500)
305 (13,900)
490 (3,900)



(8)

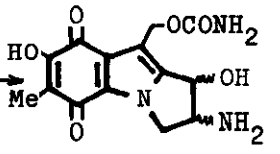
$\lambda_{max.}$(MeOH)nm(ε)
222 (24,000)
365 (214400)
513 (407)

a



(9)

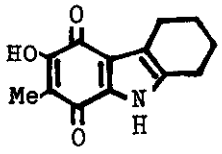
b



(10)

$\lambda_{max.}$(0.1N-HCl)nm(ε)
235 (21,700)
294 (15,900)
346 (3,920)
460 (1,050)

$\lambda_{max.}$(0.1N-NaOH)nm(ε)
254 (19,200)
312 (11,900)
560 (1,220)

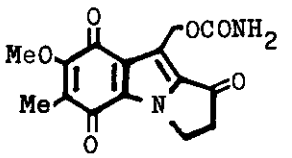


(11)

$\lambda_{max.}$(0.1N-HCl)nm(ε)
237 (20,200)
293 (19,000)
370 (4,330)
510 (1,390)

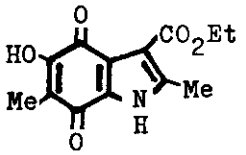
$\lambda_{max.}$(0.1N-NaOH)nm(ε)
246 (24,500)
306 (12,500)
365 (4,620)
595 (1,610)

c



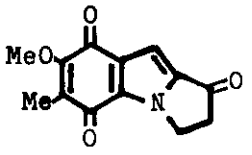
(12)

$\lambda_{max.}$(MeOH)nm(ε)
280 (41,400)



(13)

$\lambda_{max.}$(MeOH)nm(ε)
220 (21,000)
241 (15,000)
291 (14,500)
330 (6,900)
450 (540)



(14)

$\lambda_{max.}$(MeOH)nm(ε)
289 (19,000)

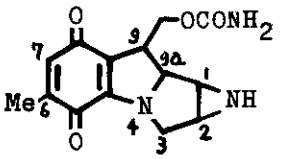
a. 0.1N-HCl b. 0.1N-NaOH c. HNO_2

X-ray structure analysis carried out by Tulinsky.[10,11] Recently, Yahashi and Matsubara[12] reported the absolute structure of mitomycin B as determined by X-ray analysis of 7-demethoxy-7-p-bromoanilinomitomycin B.

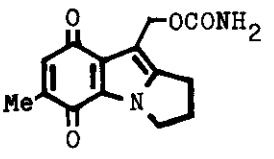
On the structure of mitiromycin, Morton et al.[13] in 1970 proposed formula (6) from analysis of the mass and n.m.r. spectra. Concerning structural studies on the mitomycins, Uzu et al.[14,15] reported a chemical degradative method, Van Lear[16] reported mass spectra, and Lown et al.[17] reported the ^{1}H- and ^{13}C-n.m.r. spectra.

The characteristics of the structure of the mitomycins make them the first naturally occurring examples of an aziridine, and the pyrrolo-[1,2-a]indole ring system with an aminobenzoquinone, urethane,[18] and angular methoxy group. Webb et al.[6] proposed the trivial name "mitosane" for the structural component (14) common to all four antibiotics.[19]

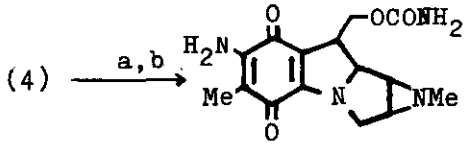
Chart 3



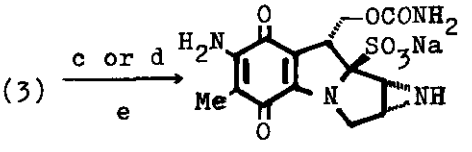
(14) Mitosane



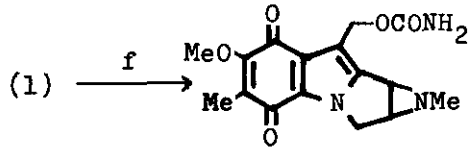
(15) Mitosene



(16)



(17)

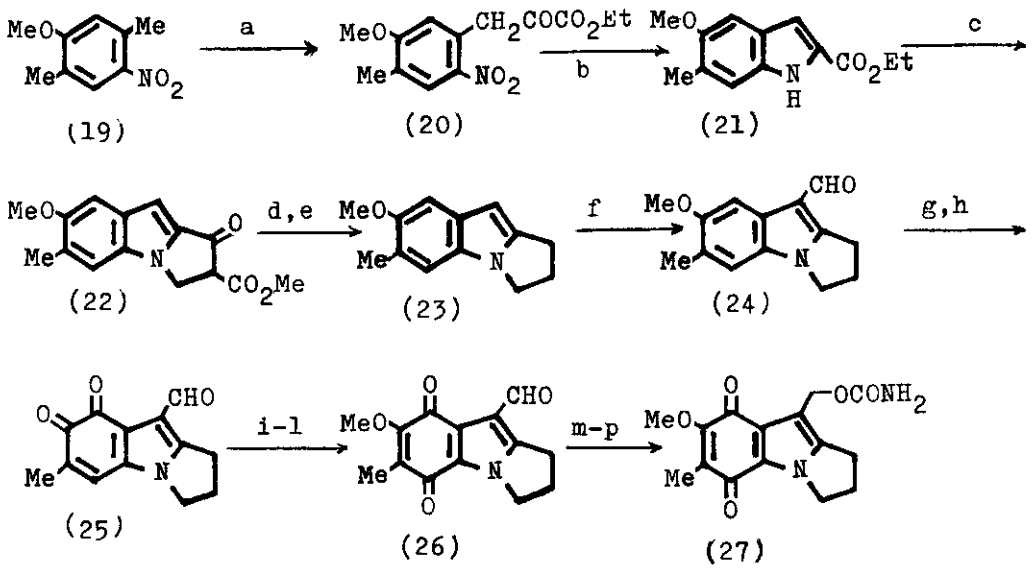


(18)

a. H_2/Pd-C
b. $ON(SO_3K)_2$
c. $Na_2S_2O_4$
d. Pd-C/Na_2SO_3
e. Pd-C/NaOMe
f. H_2/Pt→O_2

Thus mitomycin A (1) is 7,9a-dimethoxymitosane. This structure can be seen in the derivatives (16 and 17) as well as in the natural mitomycins. Namely, Kinoshita et al.[20] treated porfiromycin (4) with sodium borohydride followed by Fremy's salt to give 7-aminomitosane derivative (16). Hornemann et al.[21] prepared sodium 7-aminomitosane-9a-sulphonate (17) by the reaction of mitomycin C (3) with sodium dithionite, or with sodium sulphite in the presence of palladium-charcoal under a hydrogen atmosphere. Furthermore, they reconverted (17) to mitomycin C (3) by treatment with sodium methoxide in the presence of palladium-charcoal under a hydrogen atmosphere. This experiment constitutes the first example of the conversion of unnatural compounds to natural mitomycins.

Chart 4



a. t-BuOK/$(CO_2Et)_2$
b. Zn/HOAc
c. CH_2=$CHCO_2Me$/NaH
d. 95%HOAc
e. NH_2NH_2/KOH
f. DMF/$POCl_3$
g. $AlCl_3$
h. $ON(SO_3K)_2$
i. Ac_2O/BF_3-Et_2O
j. NaOH
k. O_2
l. CH_2N_2
m. $NaBH_4$/MeOH
n. $FeCl_3$
o. $ClCO_2Ph$/Py
p. $NH_3/CHCl_3$

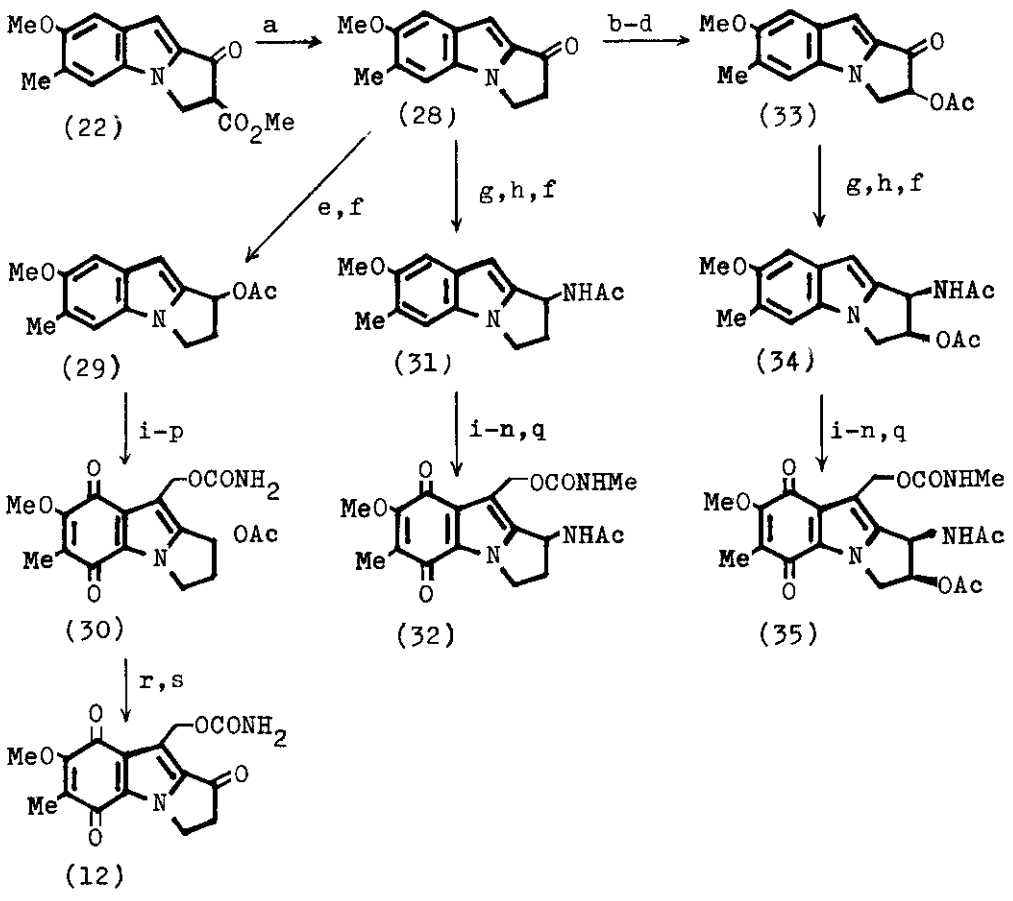
On the other hand, Webb et al. preposed the trivial name "mitosene" for the structural component common to apo-mitomycin type compounds. This structure (15) can be seen in (9 and 13) as well as in 7-methoxy-1,2-(N-methylaziridino)mitosene (18), which was prepared by Webb et al.[22] from N-methylmitomycin A (2) by catalytic reduction in the presence of platinum followed by air oxidation.[23] (Chart 3)

Until recently, synthetic studies on mitomycin related compound have been confined to mitosene derivatives, or to pyrrolo[1,2-a]indole[24-30] derivatives, because there are no efficient methods for introduction of the 9a angular methoxyl group. Weiss et al.[31] synthesised 7-methoxymitosene (27), which has the features of mitomycins without the angular methoxyl group and the aziridine ring, and found it active against Gram positive organisms. (Chart 4).

Later, studies to introduce various substituents into pyrrolo[1,2-a]-indole system,[32-34] and synthetic studies on indoloquinone derivatives[35] were extensively investigated. Remers et al. reported the synthesis of 1-acetoxy-7-methoxymitosene (30),[36] 1-acetamide-7-methoxy-N-methylmitomysene (32),[37] 1-acetamide-2-acetoxy-7-methoxy-N-methylmitosene (35)[38] and des-ammono-apo-mitomycin A (12),[37] the latter being the chemical degradation product of mitomycin A (1). Synthesis of (12) is the first example of the synthesis of a degradation product of the mitomycins but syntheses of others such as aziridinomitosene (18) and apo-mitomycin A (9) have not yet been reported. (Chart 5)

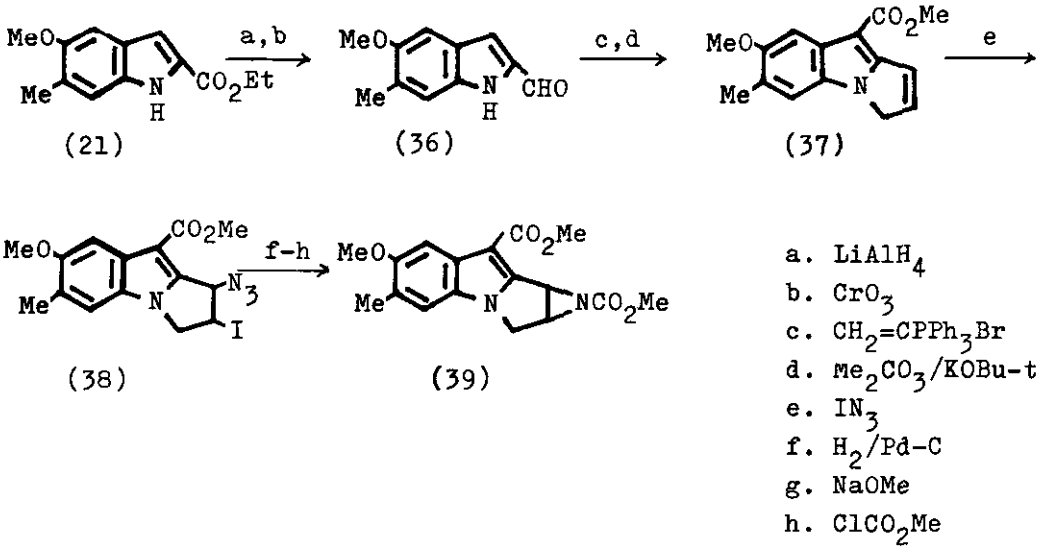
Attempts[33,39] at introduction of aziridine into pyrrolo[1,2-a]indoles have been made by Matsui et al. and by Franck et al. Matsui et al.[40] reported the synthesis of aziridinopyrrolo[1,2-a]indole (39) by reaction of the 3H-pyrrolo[1,2-a]indole derivative (37) with iodine azide to form the adduct (38), followed by the reduction of (38). (Chart 6)

Chart 5



a. 95%HOAc
b. $Me_3SiCl/ZnCl_2/Et_3N$
c. NBS/THF
d. AcOK/MeCN
e. $NaBH_4$/MeOH
f. Ac_2O/Py
g. NH_2OH
h. H_2/Pd-C
i. $DMF/POCl_3$
j. HNO_3
k. Fe/50%AcOH
l. $ON(SO_3K)_2$
m. $NaBH_4$/MeOH
n. $FeCl_3$
o. $ClCO_2Ph$/Py
p. $NH_3/CHCl_3$
q. MeNCO
r. NH_4OH
s. MnO_2

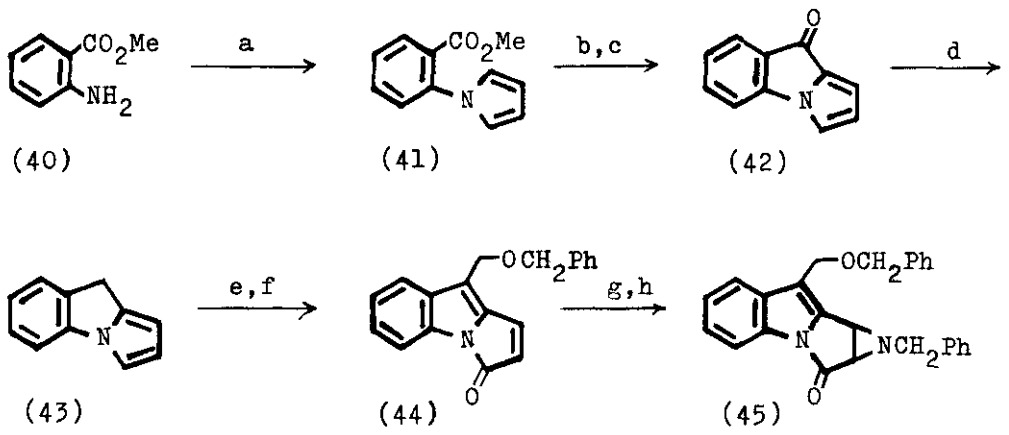
Chart 6



Franck et al. prepared the 3H-pyrrolo[1,2-a]indol-3-one derivative (44) from (43)[41] by alkylation followed by photo-oxygenation.[42] Reaction of (44) with benzyl azide followed by photolysis of the resulted triazolo derivative afforded the aziridino compound (45).[43] (Chart 7).

The first example of the introduction of the 9a methoxyl group in synthetic studies on mitomycin related compounds was achieved by the photo-oxygenation of the 9H-pyrrolo[1,2-a]indol-9-one derivative (49). Kametani et al.[44] reported the formation of (50) and (51) when (49) in methanol in the presence of rose bengal was irradiated with a halogen lamp. Hydroperoxide (50) could be converted to the alcohol (51) as shown in Chart 8.

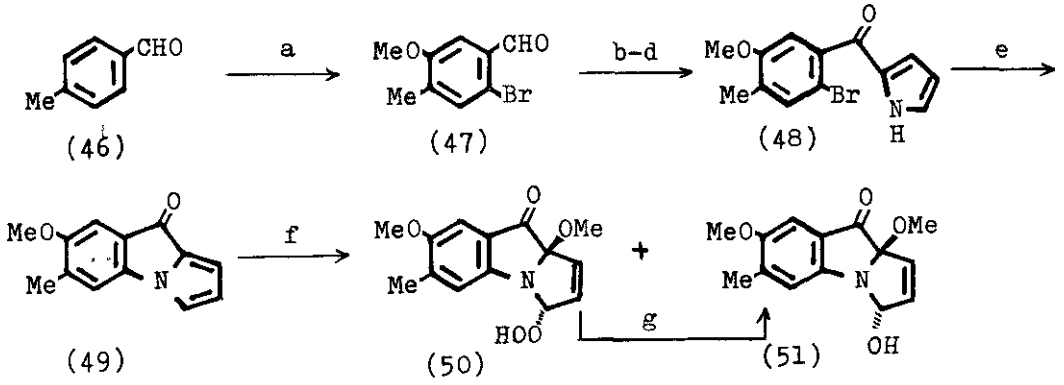
Chart 7



(40) (41) (42) (43) (44) (45)

a. 1,5-dimethoxytetrahydrofuran
b. KOH
c. $SnCl_4$
d. NH_2NH_2/KOH
e. $ClCH_2OCH_2Ph$
f. $O_2/h\nu$/methylene blue
g. $PhCH_2N_3$
h. $h\nu$

Chart 8

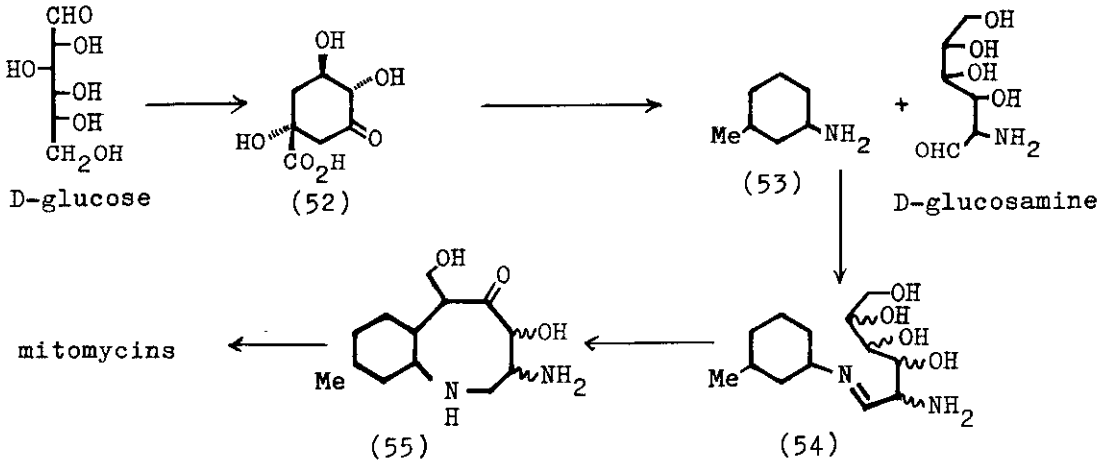


(46) (47) (48) (49) (50) (51)

a. see Chart 16
b. $KMnO_4$
c. $SOCl_2$
d. pyrrylmagnesium bromide
e. NaH/CuBr/DMF
f. $O_2/h\nu$/MeOH/rose bengal
g. Me_2S

Lown et al.[45] suggested that transannular cyclisation of the 1-benzazocin-5-one derivative (55), which can be called "seco-mitosane", will become an efficient synthetic method for the introduction of oxygen function at the C-9a position, because the biosynthetic pathway to mitomycins may contain this transannular cyclisation. Hornemann[46-50] proposed the biosynthetic pathway to mitomycins which are derived from sugar and aminosugar. That is, they showed that L-tryptophan, L-phenylalanine, L-tyrosine and shikimic acid are not incorporated into mitomycins by S. verticillatus, but that D-glucose, D-glucosamine, methionine and citrulline are incorporated. It is thought that D-glucose produces the C-seven unit (53), via dehydroquinic acid (52), and that this condenses with D-glucosamine to give (54). Lown extended Hornemann's hypothesis and speculated that transannular cyclisation of (55), produced from (54), would yield mitomycins.

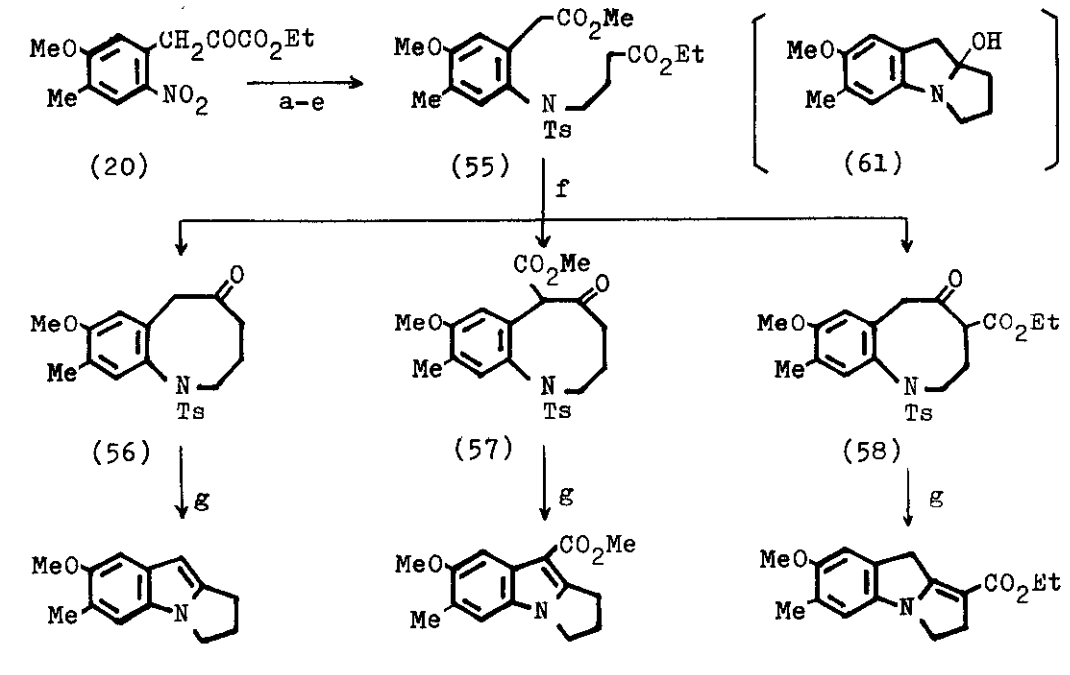
Chart 9



According to this hypothesis, Lown et al. prepared 1-benzazocin-5-one derivatives (56-58) and subjected them to conditions expected to

produce transannular cyclisation. However, the expected compound (61) could not be obtained and only dehydrated compounds (23, 59 and 60) were obtained.[45,51]

Chart 10

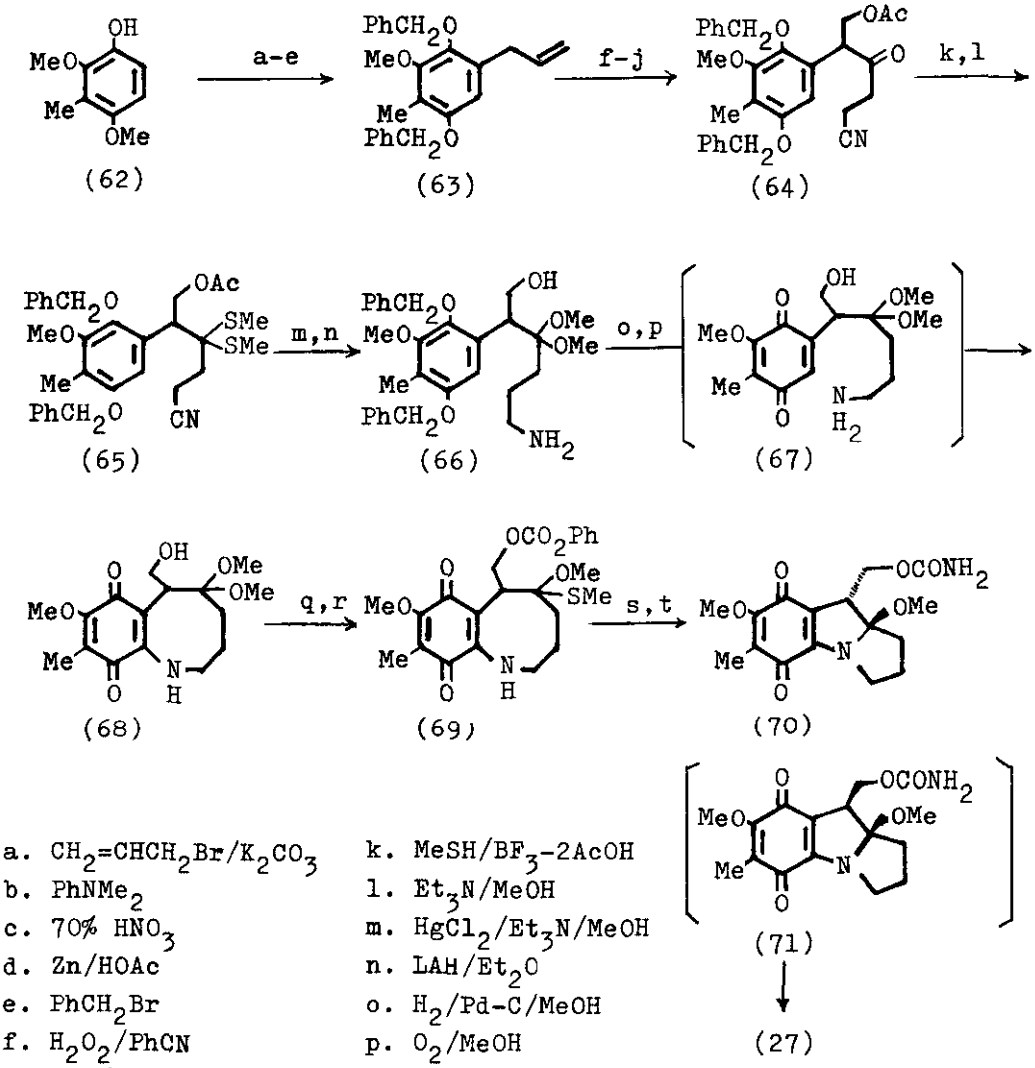


a. H_2O_2/NaOH
b. H_2SO_4/MeOH
c. H_2/Pd-C
d. TsCl
e. $Br(CH_2)_3CO_2Et$
f. t-BuOK
g. Na-NH_3

Kishi et al.[52] succeeded in the synthesis of deiminomitomycin A(70)—a mitosane type compound which has the 9a-methoxyl group—by transannular cyclisation of the "eight-membered quinone" (69), and this is the first successful synthesis of such a compound. Thus, phenol (62), obtainable from 2,6-dimethoxytoluene in 3 steps, was transformed to the amine (66) in 14 steps. Hydrogenolysis of (66) followed by treatment with oxygen afforded the eight-memberd ring compound (68), which is the product of

intramolecular Michael reaction of the quinone intermediate (67). Compound (68) was then transformed to the hemithioketal (69), and this compound was subjected to transannular cyclisation with mercuric chloride.

Chart 11



a. $CH_2=CHCH_2Br/K_2CO_3$
b. $PhNMe_2$
c. 70% HNO_3
d. Zn/HOAc
e. $PhCH_2Br$
f. $H_2O_2/PhCN$
g. LDA/MeCN
h. CrO_3/H_2SO_4
i. $NaOMe/(CH_2O)_3$
j. Ac_2O/Py
k. $MeSH/BF_3$-2AcOH
l. $Et_3N/MeOH$
m. $HgCl_2/Et_3N/MeOH$
n. LAH/Et_2O
o. H_2/Pd-C/MeOH
p. $O_2/MeOH$
q. $ClCO_2Ph/Py$
r. $MeSH/BCl_3$
s. $HgCl_2/Et_3N$
t. NH_3

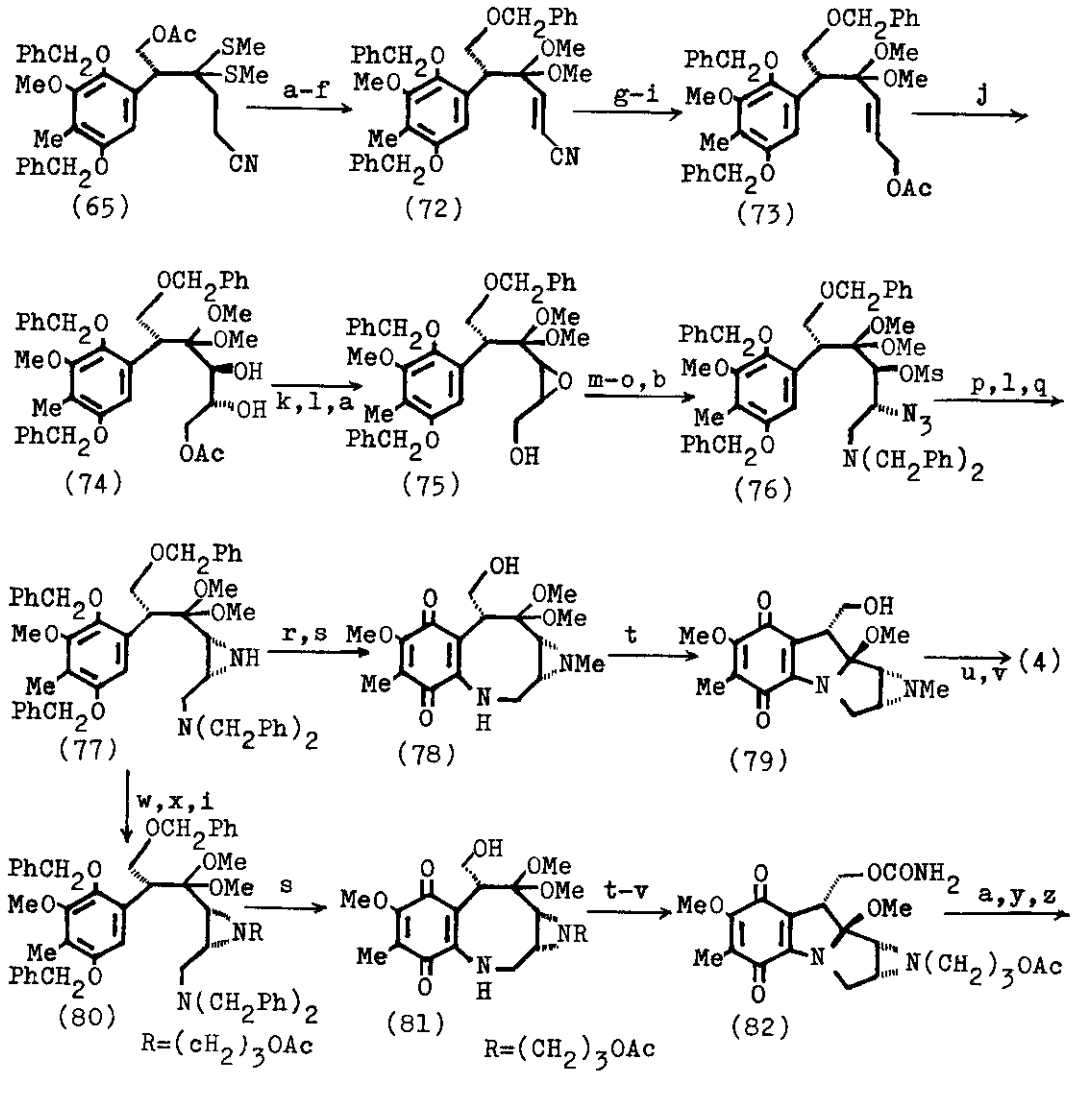
The product was treated with ammonia to yield deiminomitomycin A (70). The product from the transannular cyclisation reaction is a mixture of cis and trans isomers, but the cis isomer (71) was too unstable to isolate. Although deiminomitomycin A (70) can be isolated, it is unstable in the presence of silica gel or of catalytic amounts of acetic acid. The instability of these compounds is due to the easy elimination of methanol to form (27). (Chart 11)

Kishi et al. reported the total syntheses of porfiromycin (4)[53] and mitomycin A (1)[54] using the above transannular cyclisation. Introduction of the aziridine moiety was accomplished from the synthetic intermediate (65) of deiminomitomycin A, by way of olefin (72), diol (74) and epoxide (75). In the synthsis of porfiromycin (4), the eight-membered ring compound (78) was prerared after the nitrogen atom was methylated with methyl iodide. However in the case of the synthesis of mitomycin A, as the yield of eight-membered ring compound was low without protection of the nitrogen atom of the aziridine, it was protected with the $-(CH_2)_3OAc$ group before preparing the eight-membered ring compound (81). In the crucial steps, transannular cyclisation, ketals (78 and 81) were treated with trityl tetrafluoroborate, tetrafluoroboric acid, or perchloric acid to yield the desired compounds (79 and 82). The conditions used for the transannular cyclisation in the synthesis of deiminomitomycin A could not be applied to the cyclisation of (78) to (79) because trans-ketalisation of (78) to the corresponding hemithioketal was unsuccessful. The trityl tetrafluoroborate conditions were not successful for the synthesis of deiminomitomycin A because elimination of methanol occurred. (Chart 12).

As surveyed above, important problems in the synthesis of mitomycins are, first of all, efficient preparation of the 7-methoxy-6-methyl-pyrrolo[1,2-a]indole system, secondly, the introduction of various substituents (particularly and the aziridine ring) into this system, and finally, introduction of the 9a-oxygen function. In this thesis, facile

syntheses of the pyrrolo[1,2-a]indole system and of 7-methoxymitosene (27)[55] are described in Chapter 1, introduction of oxygen functions into the pyrrolo[1,2-a]indole system[56] and, synthesis of 3H-pyrrolo[1,2-a]indole together with preparation of desammono-apo-mitomycin A (12);[57] are described in Chapter 2, and synthesis of seco-mitosane type compounds[58-60] are reported in Chapter 3.

Chart 12

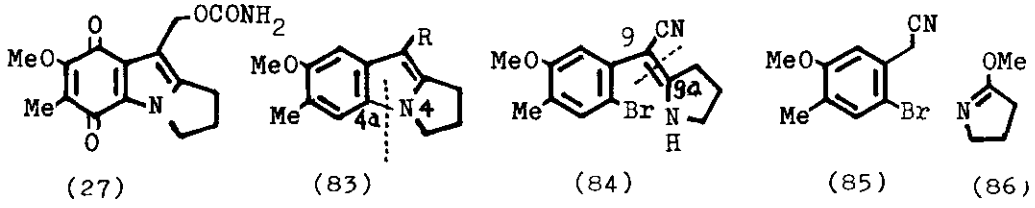


a. NaOMe/MeOH
b. $PhCH_2Br$
c. $HgCl_2$/MeOH
d. LDA/THF
e. PhSeBr
f. H_2O_2
g. i-Bu_2AlH
h. $NaBH_4$/MeOH
i. Ac_2O/Py
j. OsO_4
k. MsCl/Et_3N
l. NaH
m. LiN_3/DMF
n. Ms_2O/Py
o. $PhCH_2NH_2$
p. $P(OMe)_3$
q. LAH
r. MeI/K_2CO_3
s. H_2/Pd-C→O_2
t. Ph_3CBF_4
u. $COCl_2$
v. NH_3
w. CH_2=CHCHO
x. BH_3/THF
y. DMSO/DCC
z. $HClO_4$/$PhNMe_2$

CHAPTER 1 SYNTHESIS OF 7-METHOXYMITOSENE

In the area of synthetic studies on mitomycins, one of the most important problems, as already described, seems to be the preparation of mitosene derivatives. Synthesis of 7-methoxymitosene (27) requires the 9-substituted 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole system (83) (R=CHO, CN, or CO_2Me; which can be easily converted to the $-CH_2OCONH_2$ group).[61] However, there are few reported procedures[24] for the synthesis of this system which are satisfactory both from the point of view of yield and of number of steps. Therefore the author first examined synthetic routes to this system. From the structure of (83), its synthetic precursor could be (84) if ring closure is effected at the 4-4a positions. For the preparation of (84), condensation of phenylacetonitrile (85) with 2-methoxy-Δ^1-pyrroline (86)[62] was thought to be a possibility.

Chart 13

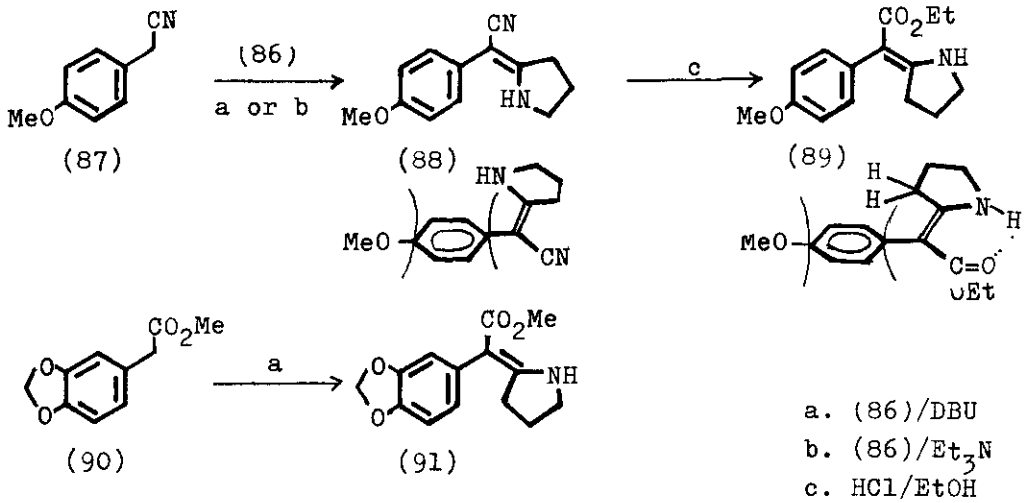


(27) (83) (84) (85) (86)

In the preliminary experiment, heating 2-methoxy-Δ^1-pyrroline (86) with the arylacetonitrile (87)[63] in the presence of triethylamine or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) at 100-120°C gave the corresponding α-aryl-α-pyrrolidin-2-ylideneacetonitrile (88) in good yield.[64] However, condensation of 2-methoxy-Δ^1-pyrroline (86) with methyl 3,4-methylenedioxyphenylacetate (90)[65] gave a pyrrolidinylideneacetate (91) in low yield, on heating with DBU. Refluxing the pyrrolidinylideneacetonitrile (88) with ethanol previously saturated with dry hydrogen chloride gas[66] gave the corresponding ethyl pyrrolidinylideneacetate (89). The α-aryl-α-

pyrrolidin-2-ylideneacetates(89 and 91) showed i.r. absorptions due to NH at 3350 and to ester at 1640 cm^{-1}. Their n.m.r. spectra showed the NH signals at δ 8.40-8.50 (broad singlet) and the pyrrolidine 3-H_2 signals at δ 2.42-2.46 (triplet, J 6Hz). The nitrile (88) showed i.r. absorptions at 3450 (NH) and 2180 cm^{-1} (CN). Its n.m.r. spectrum showed the NH signal at δ 4.80-5.50 (broad singlet) and the pyrrolidine 3-H_2 signal at δ 2.95 p.p.m. (triplet, J 6Hz). In the light of the above observation, hydrogen bonding between the NH and the ester groups is expected for the acetates (89 and 91). Therefore these acetates are thought to exist in the Z-form, in which the pyrrolidine 3-protons are shielded by the aryl group. The nitrile, showing no such shielding, may well exist in the E-form. This assignment is in complete agreement with the result of experiment carried out by Onaka.[67]

Chart 14

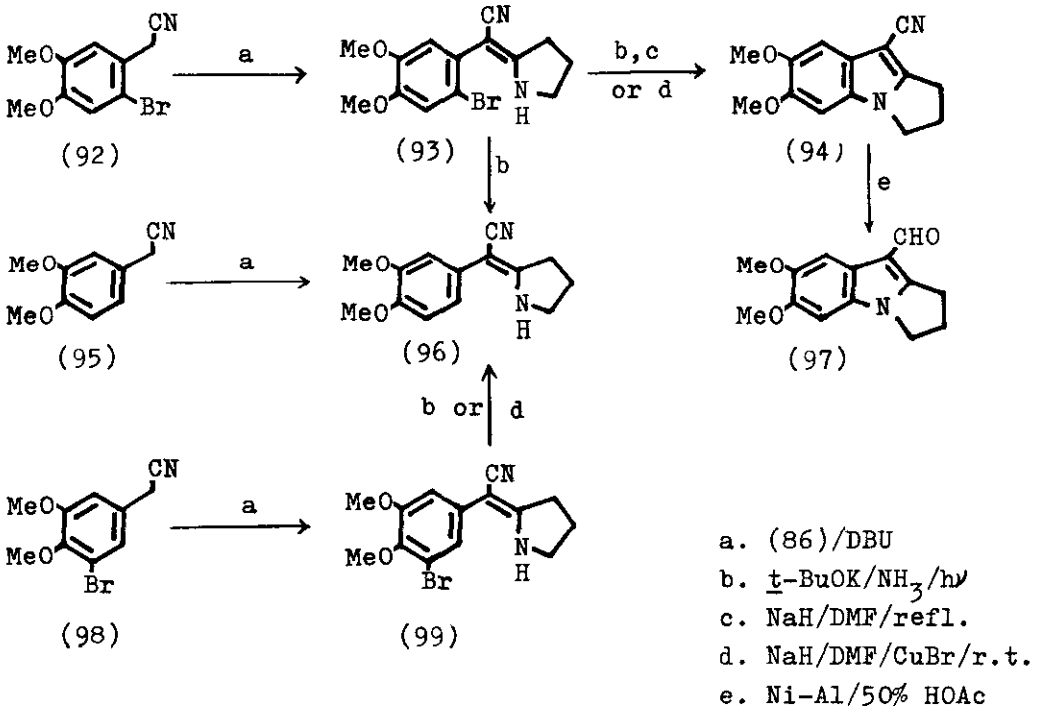


a. (86)/DBU
b. (86)/Et_3N
c. HCl/EtOH

As the condensation of 2-methoxy-Δ^1-pyrroline (86) with phenylacetonitrile (87) gave successful results, the condensation of (86) with o-bromophenylacetonitrile derivative (92),[68] readily available from vanillin, was examined. This yielded the condensation product (93), which was subjected to a variety of ring closure conditions. In the unactivated

aromatic ring which has no electron-withdrawing substituents, the direct displacement of halogen by a nucleophile demands drastic conditions ; but several modified nucleophilic aromatic substitutions have been reported recently.[69-74] The formation of pyrrolo[1,2-a]indole by a route involving an intramolecular nucleophilic aromatic substitution was attempted. Thus, although cyclisation did not occur when (93) was treated with sodium amide in liquid ammonia, irradiation of (93) in liquid ammonia in the presence of potassium t-butoxide afforded (94) in 2 % yield by a photo-induced $S_{RN}1$ reaction,[69,70] with debrominated compound (96)[75] as the main product. Refluxing (93) with sodium hydride in dry dimethylformamide, followed by chromatographic purification, gave the desired pyrrolo[1,2-a]-indole (94) in 70 % yield. The reaction was catalysed by copper (I)

Chart 15

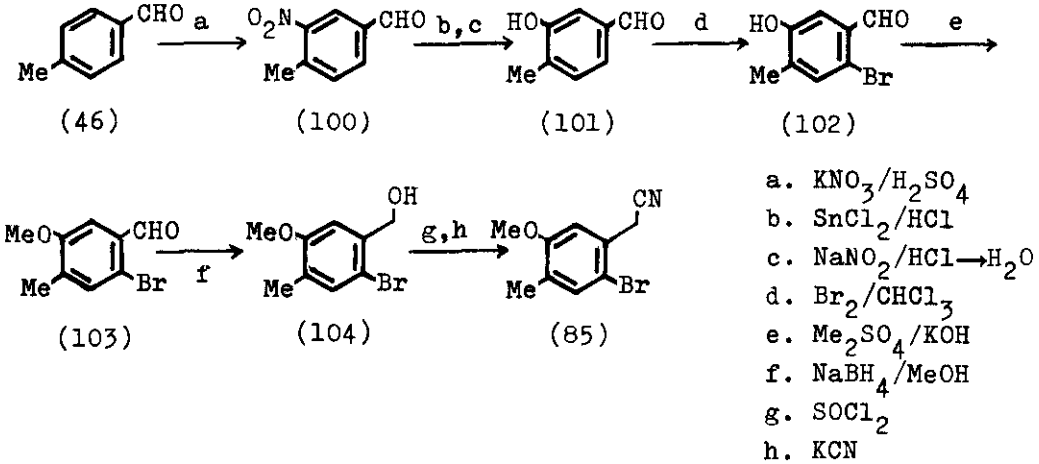


a. (86)/DBU
b. t-BuOK/NH_3/hν
c. NaH/DMF/refl.
d. NaH/DMF/CuBr/r.t.
e. Ni-Al/50% HOAc

bromide.[71,72] Thus treatment of (93) with an equimolar amount of sodium hydride in the presence of copper (I) bromide in dry dimethylformamide at room temperature for 3h afforded (94) in 90 % yield. In the above reactions, a benzyne mechanism is not probable because heating the 3-bromo-4,5-dimethoxyphenyl analogue(99)[76] with sodium hydride in dry dimethylformamide in the presence, or in the absence, of copper (I) bromide gave none of the cyclised compound (94), with only starting material (99) and the debrominated compound (96) being isolated from a tarry product. Refluxing the nitrile (94) with nickel-aluminium alloy in 50 % aqueous acetic acid[77] gave the aldehyde (97) in 91 % yield. Replacement of aqueous acetic acid by aqueous formic acid[78] in this reaction gave an unsatisfactory result.

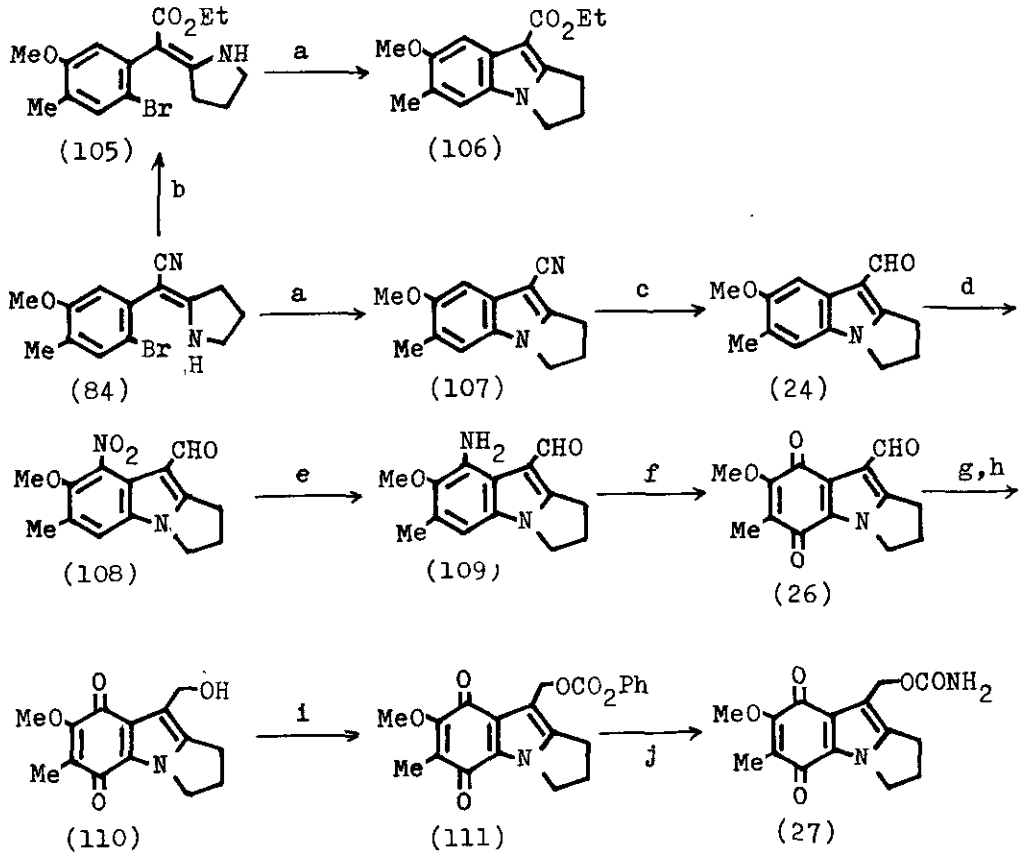
2-Bromo-5-methoxy-4-methylphenylacetonitrile (85), which has the required substituents for 7-methoxymitosene synthesis, was prerared from commercially available p-tolualdehyde (46) in eight steps as follows. Nitration of the aldehyde (46) with potassium nitrate yielded the nitro compound (100),[79] which was transformed by reduction[80] followed by di-

Chart 16



azotisation to the phenol (101).[81] Bromination of the phenol (101) yielded the bromide (102), which was methylated with dimethyl sulphate to give the aldehyde (103).[82] Reduction of (103) with sodium borohydride, followed by chlorination of the resulting alcohol (104) with thionyl chloride, and cyanation with potassium cyanide in the presence of sodium iodide in ethyl methyl ketone, gave the nitrile (85) in 69 % yield from (103).

Chart 17



a. NaH/CuBr/DMF
b. HCl/EtOH
c. Ni-Al/50% HOAc
d. HNO_3/HOAc
e. Fe/50% HOAc
f. $ON(SO_3K)_2$
g. $NaBH_4$/MeOH
h. $FeCl_3$
i. $ClCO_2Ph$/Py
j. $NH_3/CHCl_3$

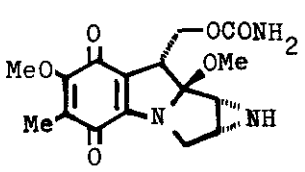
The nitrile (85) thus obtained was converted to the condensation product (84). Treatment of (84) with ethanol saturated with hydrogen chloride gas afforded the ester (105). The nitrile (84) and the ester (105) on treatment with sodium hydride and copper (I) bromide in dry dimethylformamide gave the cyclised products (107) and (106), respectively, in excellent yield. The nitrile (107) afforded the aldehyde (24) on reaction with nickel-aluminium alloy in aqueous acetic acid. Weiss *et al.*,[31] as shown previously in Chart 4, transformed the aldehyde (24) to the *p*-quinone (26) by way of the *o*-quinone (25). The author synthesised the *p*-quinone (26) from the aldehyde (24) by nitration followed by reduction of (108) and then oxidation of the resulting amine (109) with Fremy's salt. The melting point and spectral data of (26) were identical to those already reported. According to Weiss's procedure, sodium borohydride reduction of (26) followed by oxidation with ferric chloride was carried out to afford the quinone-alcohol (110). 7-Methoxymitosene (27) was prepared from (110) *via* the phenyl carbonate derivative (111). The melting point and spectral data of (27) were identical to those already reported.

CHAPTER 2 INTRODUCTION OF OXYGEN FUNCTIONS INTO THE PYRROLO[1,2-a]-INDOLE SYSTEM

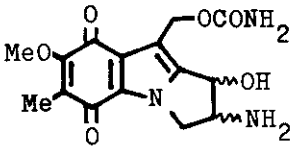
Part 1 Reaction of Pyrrolo[1,2-a]indoles with N-Bromosuccinimide in Protic Solvents.

Comparing the structural formula of mitomycin A (1) or apo-mitomycin A (9) with the pyrrolo[1,2-a]indole skeleton (112) shows that the introduction of oxygen functions into pyrrolo[1,2-a]indole is an important problem in the synthetic studies of mitomycins.

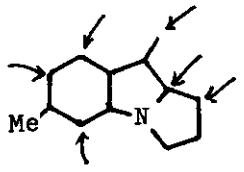
Chart 18



(1)



(9)



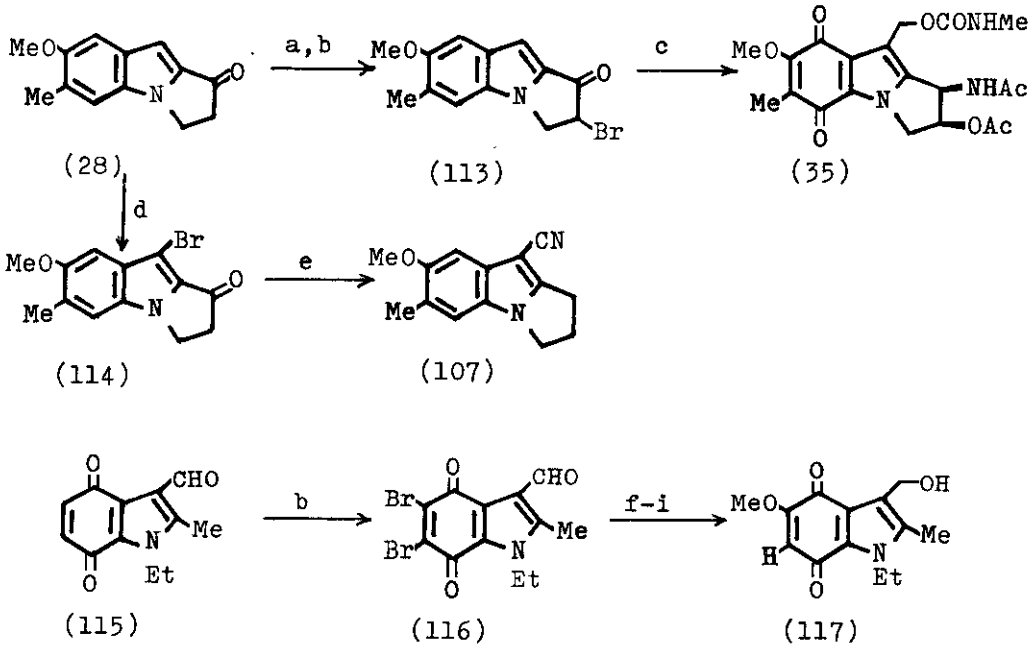
(112)

Bromination of pyrrolo[1,2-a]indoles such as (28) [synthetic intermediate of (35)[38] shown in Chart 5] and indoloquinone (115)[83] is known to be a highly efficient method for functionallisation of these nuclei in the synthesis of mitomycin related compounds. (Chart 19).

On the other hand, it is well known that reactions of indole derivatives (118[84] or 120[85]) with N-bromosuccinimide (NBS) in protic solvents give interesting results. Therefore reaction of pyrrolo[1,2-a]-indole derivatives with NBS in protic solvents, was expected to provide some useful procedures for the synthesis of mitomycin related compouns, especially those having 9a-oxygen functions. (Chart 20).

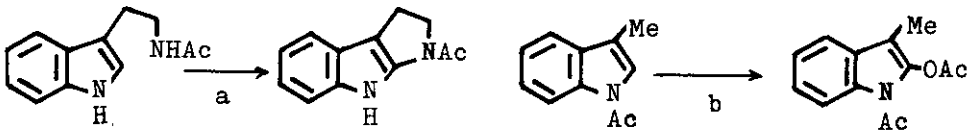
Treatment of 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carbonitrile (107) with NBS in methanol gave 8-bromo-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carbonitrile (122) and 5-bromo-2,3-dihydro-7,8-dimethoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carbonitrile (123). The structure of the latter compound was initially assigned as

Chart 19



a. Me_3SiCl
b. Br_2
c. cf.Chart 5
d. HBr/Br_2
e. CuCN
f. NaOH
g. CH_2N_2
h. $NaBH_4$/MeOH
i. $FeCl_3$

Chart 20

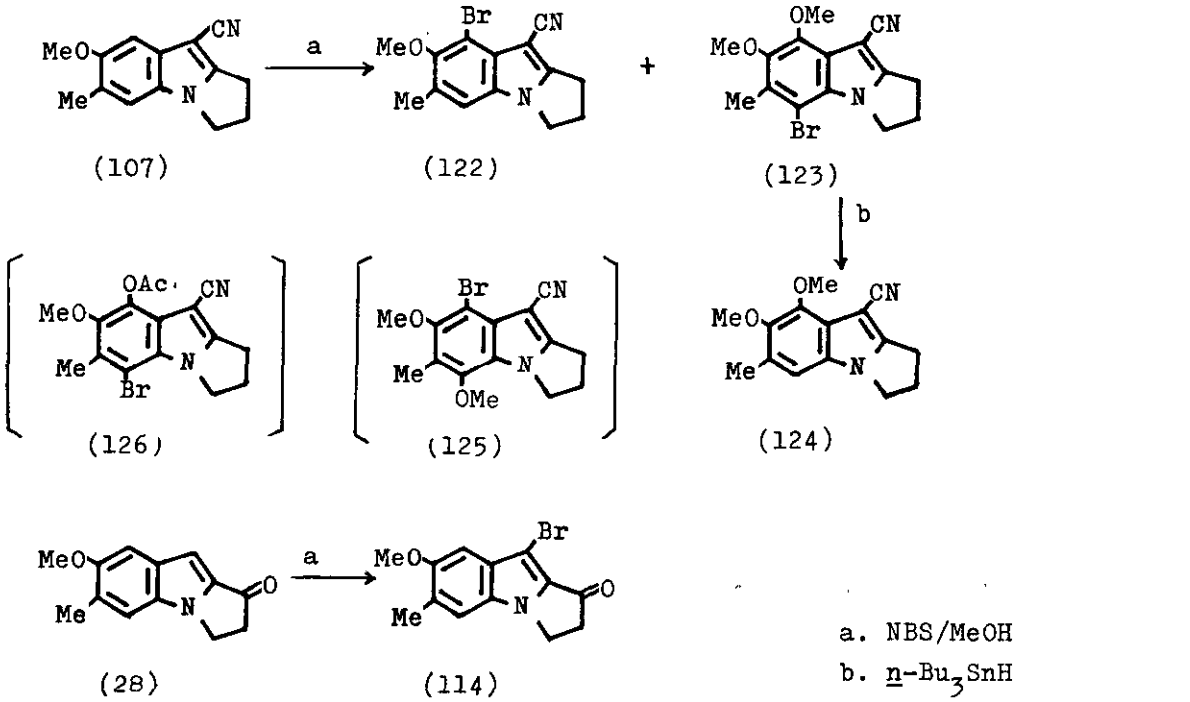


a. NBS/H_2O b. NBS/HOAc

formula (125). However, debromination of the compound revealed that the structure should be corrected to (123). Thus, the compound was heated

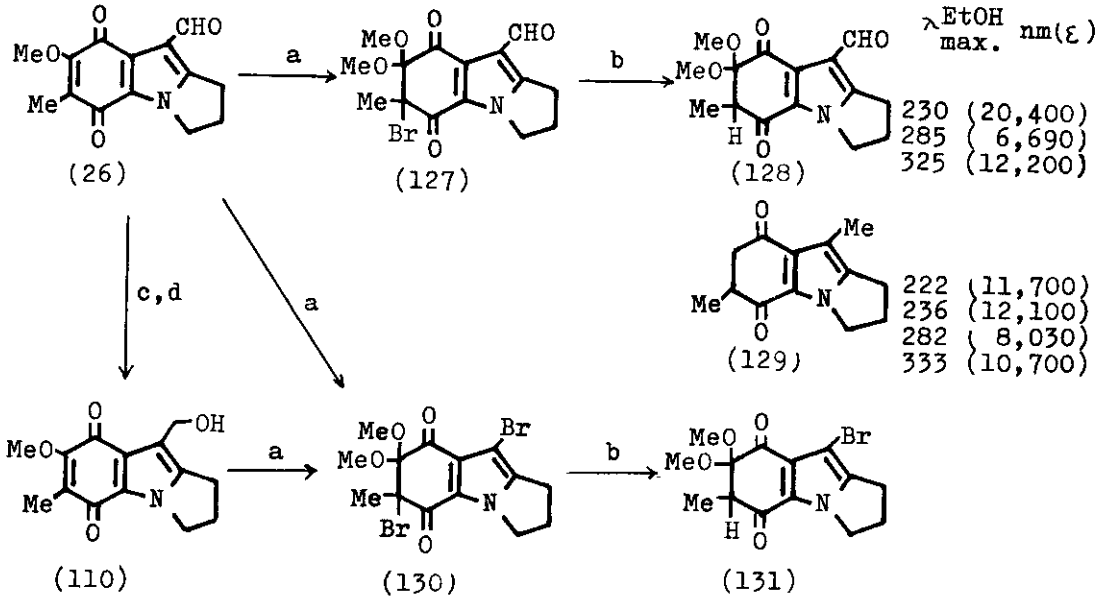
with tri-n-butyltin hydride in benzene in the presence of azobisisobutyronitrile.[86] The resonance signal of the methylene protons at the 3-position of the debrominated compound (124) was observed at 4.08 p.p.m. in the n.m.r. spectrum, while that of those protons of the starting material (123) appeared at 4.56 p.p.m. Such a great difference in the chemical shift would indicate that the bromine atom was present at the 5-position. Bromination of the nitrile (107) with NBS in acetic acid furnished (122) as the sole product with no corresponding acetoxy compound (126) being obtained. Treatment of the ketone (28) with one molar equivalent of NBS in methanol afforded the compound (114), which had bromine at the 9-position, in good yield. The spectral data were consistent with those previously reported.[32]

Chart 21



Then the reaction of some pyrrolo[1,2-a]indole-5,8-diones with NBS in protic solvents was investigated. When the aldehyde-quinone (26) was treated with a slight excess of NBS in methanol-dichloromethane (1:1 v/v) at room temperature for 1 h, the adduct[87] (127) was obtained. Introduction of bromine and methoxyl group to C-6 and C-7 positions respectively, was suggested by the u.v. spectrum, which is similar to that of the 2,3,6,7-tetrahydropyrrolo[1,2-a]indole-5,8-dione (129) which has been reported by Takada et al.[88] This structure for the adduct was further supported by the debromination of (127). Namely, treatment of the adduct (127) with tri-n-butyltin hydride in the presence of azobisisobutyronitrile afforded the debrominated compound (128) whose resonance signal of the methyl protons at the 6-position was observed as a doublet (J 7 Hz) at 1.20 p.p.m. in the n.m.r. spectrum. On treatment of the alcohol (110) with an excess of NBS in methanol, the dibromide (130) was obtained, while

Chart 22

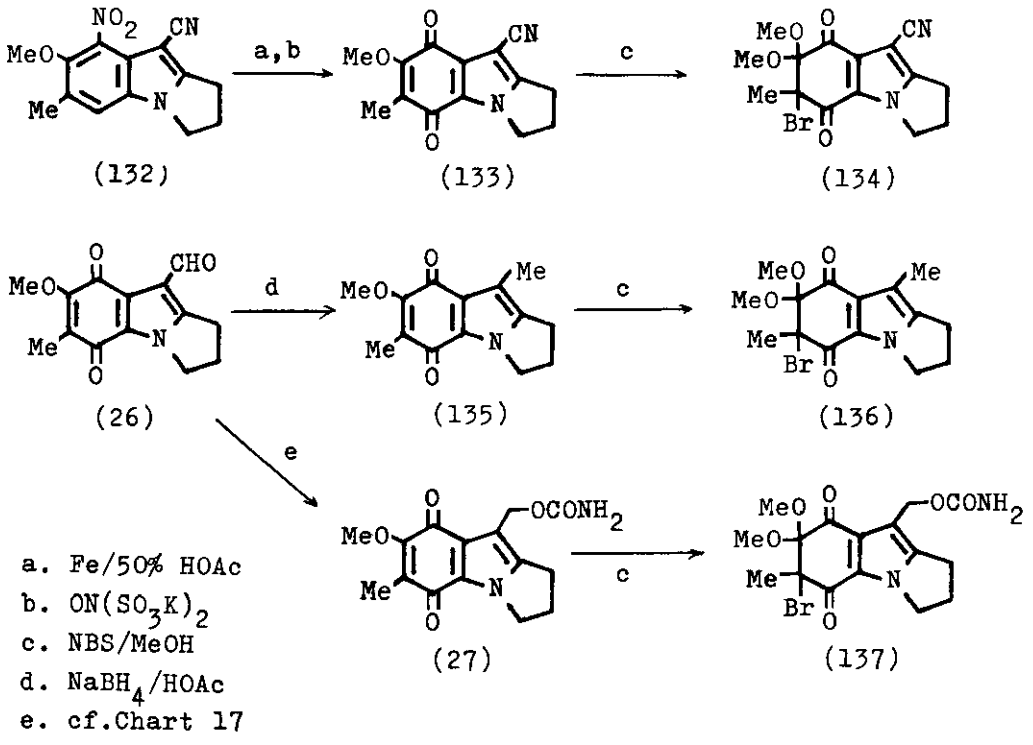


a. NBS/MeOH b. n-Bu_3SnH c. $NaBH_4$/MeOH d. $FeCl_3$

reaction using one equivalent of NBS gave an unseparable mixture of (130) and the starting material. The dibromide (130) was also obtained by treatment of the aldehyde (26) with a large excess of NBS for a long time. The dibromide (130) was treated with tri-n-butyltin hydride to give the monobromide (131).

Similar adducts (134,136 and 137) were obtained from the nitrile-quinone (133), the 6,9-dimethyl-quinone (135) and the 7-methoxymitosene (27), respectively. In these experiment, (133) was prepared by the usual method from the nitrile (107); nitration of (107), followed by reduction of the nitro compound (132) and oxidation of the resulting amine with Fremy's salt. 6,9-Dimethyl-quinone (135) was prepared from the aldehyde-quinone (26) by treatment with sodium borohydride in acetic acid.[89] In this reaction it is interesting that the quinone part of (26) was not

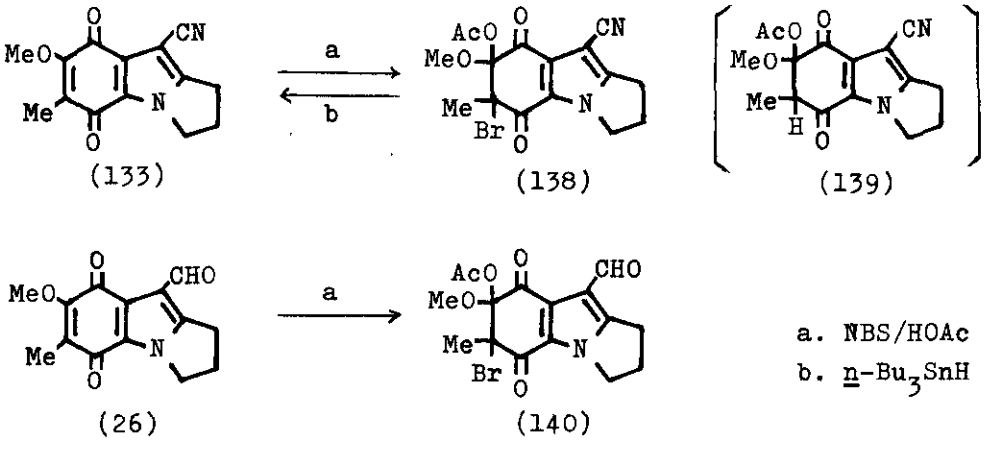
Chart 23



reduced under the above conditions.

When the reaction with NBS was carried out in acetic acid, (133) and (26) yielded the 7-acetoxybromides (138 and 140), respectively. Thus, treatment of the nitrile (133) with NBS in acetic acid-dichloromethane (1:1 v/v) at room temperature for 15 h gave the acetate (138). The aldehyde (26) gave the acetate (140) under the same conditions. Attempted debromination of (138) with tri-n-butyltin hydride afforded none of the debrominated compound (139) but gave the original quinone (133) which can be regarded as the product of elimination of acetic acid from (139). This reversible reaction may prove to be of use for protection of the quinone group in this case.

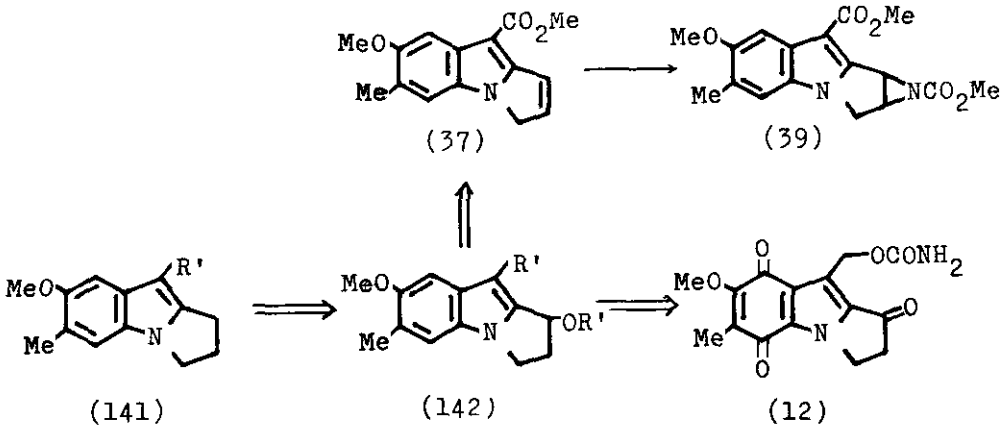
Chart 24



Part 2 Synthesis of 3H-Pyrrolo[1,2-a]indole and Desammono-apo-mitomycin A

Introduction of an oxygen function into the 1-position of 2,3-dihydro-1H-pyrrolo[1,2-a]indoles (141) is expected to make possible the preparation of 3H-pyrrolo[1,2-a]indole derivatives by an elimination reaction.[32,90] As it should also enable the synthesis of desammono-apo-mitomycin A (12), introduction of oxygen functions into the 1-position of such compounds was examined.

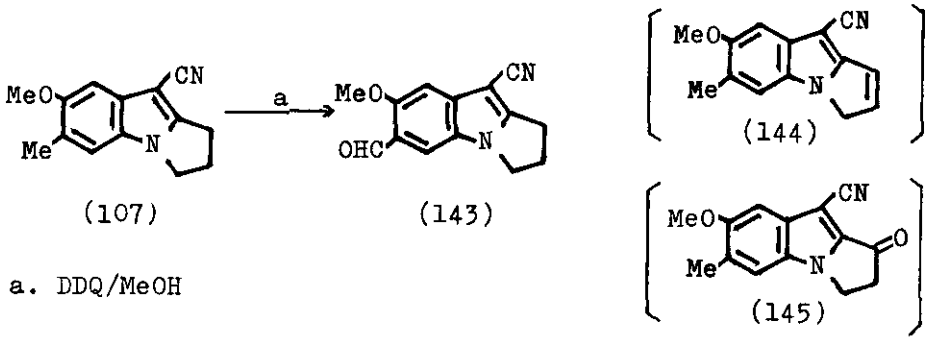
Chart 25



Firstly, oxidative reactions on the 2,3-dihydro-1H-pyrrolo[1,2-a]-indole-9-carbonitrile (107) were examined. Treatment of (107) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene or dioxane however did not yield the expected dehydrogenation product (144). Reaction of (107) with 2 equivalents of DDQ in methanol[91] also did not produce the expected ketone (145) but afforded the aldehyde (143) in 71 % yield.

Introduction of a substituent at the C-1 position was achieved by using lead tetraacetate.[92] Thus, stirring compound (94) with 1 equiv-

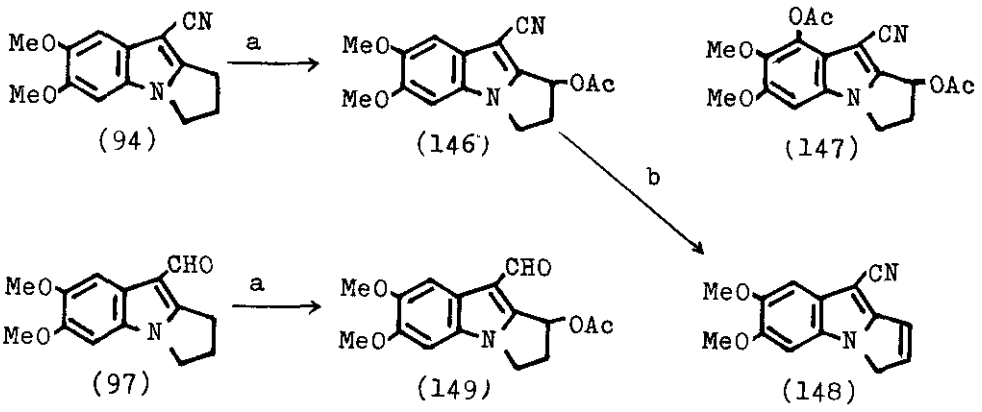
Chart 26



a. DDQ/MeOH

alent of lead tetraacetate in acetic acid at room temperature afforded the 1-acetoxy compound (146) in 76 % yield. However, reaction of (94) with 2 equivalent of lead tetraacetate in acetic acid at 90-100°C furnished a tarry product from which 1,8-diacetoxy-2,3-dihydro-6,7-dimethoxy-1H-pyrrolo[1,2-a]indole-9-carbonitrile (147) was isolated in 11 % yield. The 2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (97) was then acetoxylated by treatment with 1 equivalent of lead tetraacetate in acetic acid at room temperature to give (149) in 65 % yield. The 1-

Chart 27



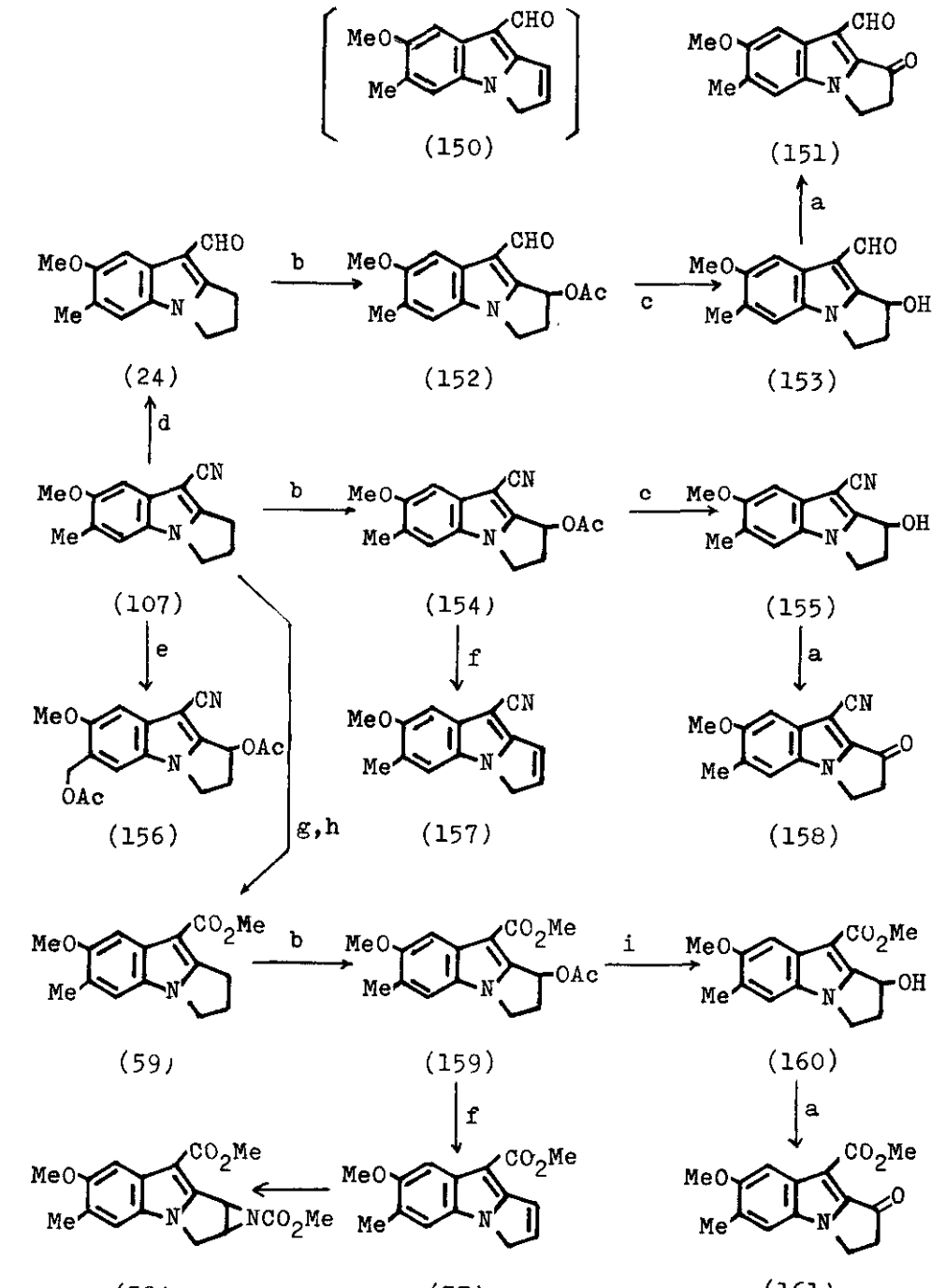
a. $Pb(OAc)_4$/HOAc/r.t.
b. HOAc/100°C

acetoxy compound (146) yielded the 3H-pyrrolo[1,2-a]indole derivative (148) on heating in acetic acid at 100°C.

Similar reactions were carried out with 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indoles (24, 107 and 59) to give the corresponding acetates (152, 154 and 159), respectively. The ester (59) was prepared from the nitrile (107) by hydrolysis with potassium hydroxide followed by treatment of the acid with diazomethane. Use of excess lead tetra-acetate at high temperature on (107) did not give the 1,8-diacetoxy compound but gave (156), by acetoxylation of the 6-methyl group. The 1-acetoxyl groups of compounds (152, 154 and 159) were selectively hydrolysed with sodium hydrogen carbonate in methanol to afford the 1-hydroxy compounds (153, 155 and 160), respectively. These alcohols were transformed, by oxidation with activated manganese dioxide,[93] to the ketones (151, 158 and 161), respectively. It should be possible to introduce a substituent at the 2-position using this ketone carbonyl function.[33] Furthermore, heating the acetates (154 and 159) in acetic acid afforded the 3H-pyrrolo[1,2-a]indoles (157 and 37), although (150) could not be obtained from the aldehyde (152) on similar treatment. Matsui et al.[40] had already transformed the ester (37) to the tetracyclic aziridino-pyrrolo]1,2-a]indole (39). (Chart 28).

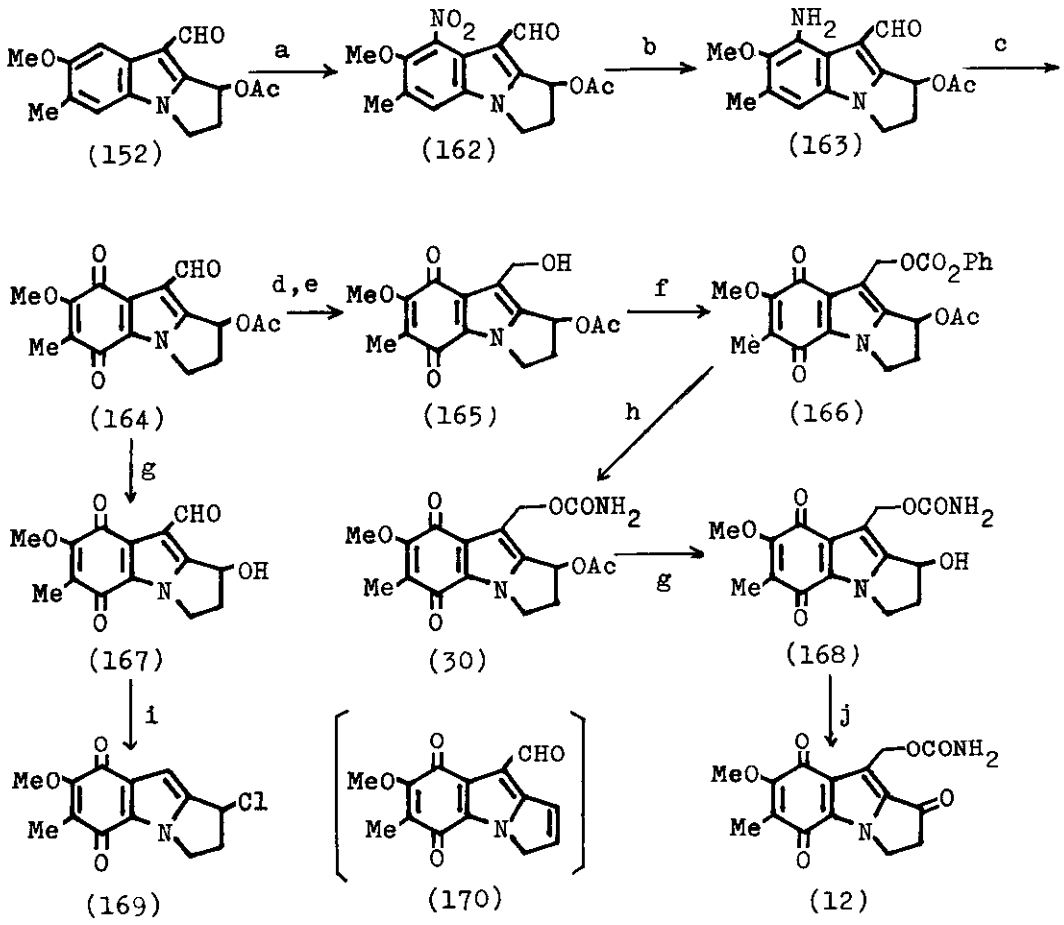
1-Acetoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole (152) was converted to the 1-acetoxy-7-methoxymitosene (30), via the nitro compound (162) and the amine (163), by Remers' procedure.[37] The acetoxyl group of the quinone (164) was hydrolysed to give the alcohol (167), which was converted to the chloride (169) by reaction with lithium chloride and mesyl chloride in dimethylformamide.[94] Attempted synthesis of (170) from the alcohol (167) by dehydration, or from the chloride (169) by elimination of hydrogen chloride failed. 1-Acetoxy-7-methoxymitosene (30) afforded the alcohol (168), on hydrolysis with sodium hydrogen carbonate in methanol, and its melting point and spectral data were identical to those already reported. As the synthesis of the desammono-apo-mitomycin A, has already

Chart 28


(150)
(151)
(24)
(152)
(153)
(107)
(154)
(155)
(156)
(157)
(158)
(59)
(159)
(160)
(39)
(37)
(161)
a. MnO_2/CH_2Cl_2
b. $Pb(OAc)_4$/HOAc/r.t.
c. KOH/MeOH
d. Ni-Al/50% HOAc
e. $Pb(OAc)_4$/HOAc/100°C
f. HOAc/100 C
g. KOH/ethyleneglycole
h. CH_2N_2
i. $NaHCO_3$/MeOH

been reported by Remers,[37] by treatment of the alcohol (168) with activated manganese dioxide, formal synthesis of (12) was completed.

Chart 29



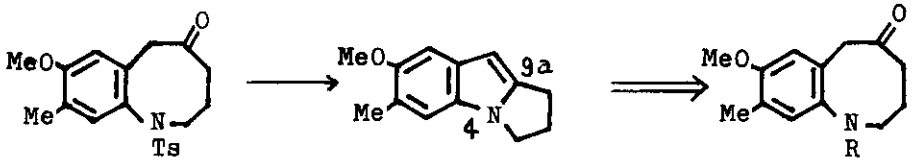
a. HNO_3/HOAc
b. Fe/50% HOAc
c. $ON(SO_3K)_2$
d. $NaBH_4$/MeOH
e. $FeCl_3$
f. $ClCO_2Ph$/Py
g. $NaHCO_3$/MeOH
h. NH_3/CH_2Cl_2
i. LiCl/MsCl/DMF
j. MnO_2/CH_2Cl_2

CHAPTER 3 SYNTHESIS OF SECO-MITOSANE TYPE COMPOUNDS

Part 1 Conversion of 2,3-Dihydro-1H-pyrrolo[1,2-a]indoles into 1-Benzazocin-5-ones.

As already described, Lown and Itoh[45] have reported the synthesis of 2,3-dihydro-1H-pyrrolo[1,2-a]indole (23) by the transannular cyclisation of the 1-benzazocin-5-one (56), according to the biosynthetic pathway. It seemed to be significant to transform the 2,3-dihydro-1H-pyrrolo[1,2-a]-indole (23), the important synthetic intermediate of 7-methoxymitosene (27), into 1-benzazocin-5-one derivative (171), because such a conversion relates the previous synthetic studies on mitosenes to the transannular cyclisation of the 1-benzazocin-5-one derivatives that enabled the total syntheses[54,55] of mitomycins.

Chart 30

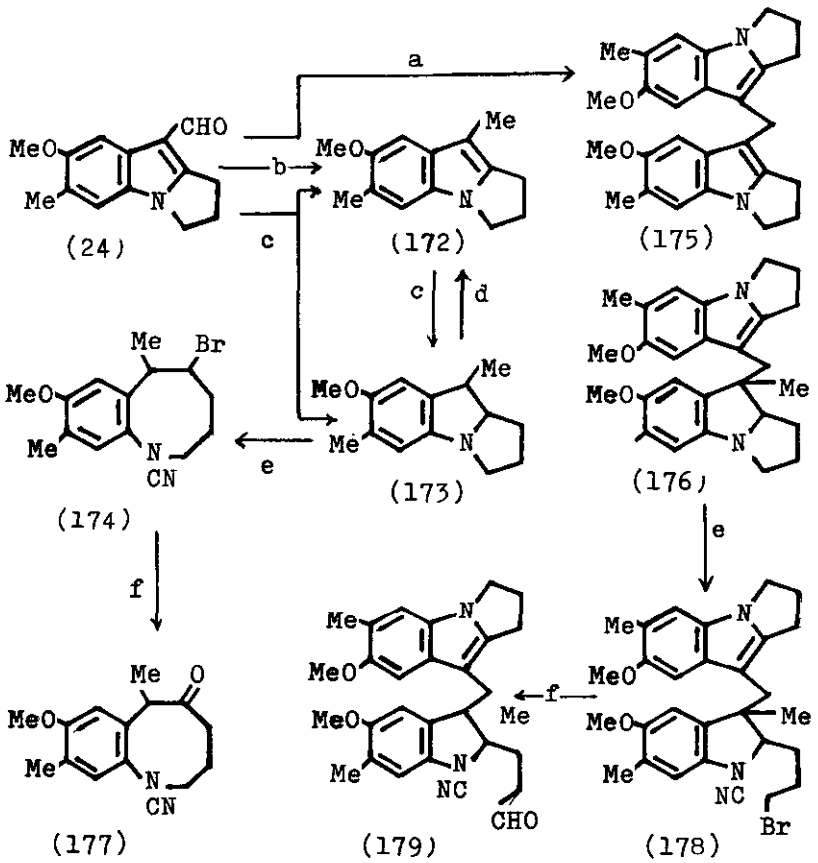


(56) (23) (171)

If von Braun type reaction[95,96] is to be applied for the ring cleavage at the 4-9a bond of the pyrroloindole, it is first necessary to reduce the 9-9a double bond to form an indoline. This reduction was accomplised with sodium borohydride in acetic acid.[89] Reaction of the aldehyde (24) with sodium borohydride in glacial acetic acid at 25-30°C gave a mixture of the indolines (173 and 176) as main products, together with indoles (172 and 175) as minor ones, and the mixture was separated by high performance liquid chromatography. Compound (172) was obtained by Wolff-Kishner reduction of the aldehyde (24) as well as by treatment

of the indoline (173) with activated manganese dioxide.[97] Reduction of the indole (172) with sodium borohydride in acetic acid afforded the indoline (173) as the sole product, and reduction of the aldehyde (24) with sodium borohydride in methanol afforded (175) as the sole product.[61] On treatment of the above mixture of the indolines, obtained from (24), with cyanogen bromide, compounds (173 and 176) gave the ring-opened bromides (174 and 178),[98] respectively. These bromides were separated by silica gel column chromatography and the structures were determined

Chart 31

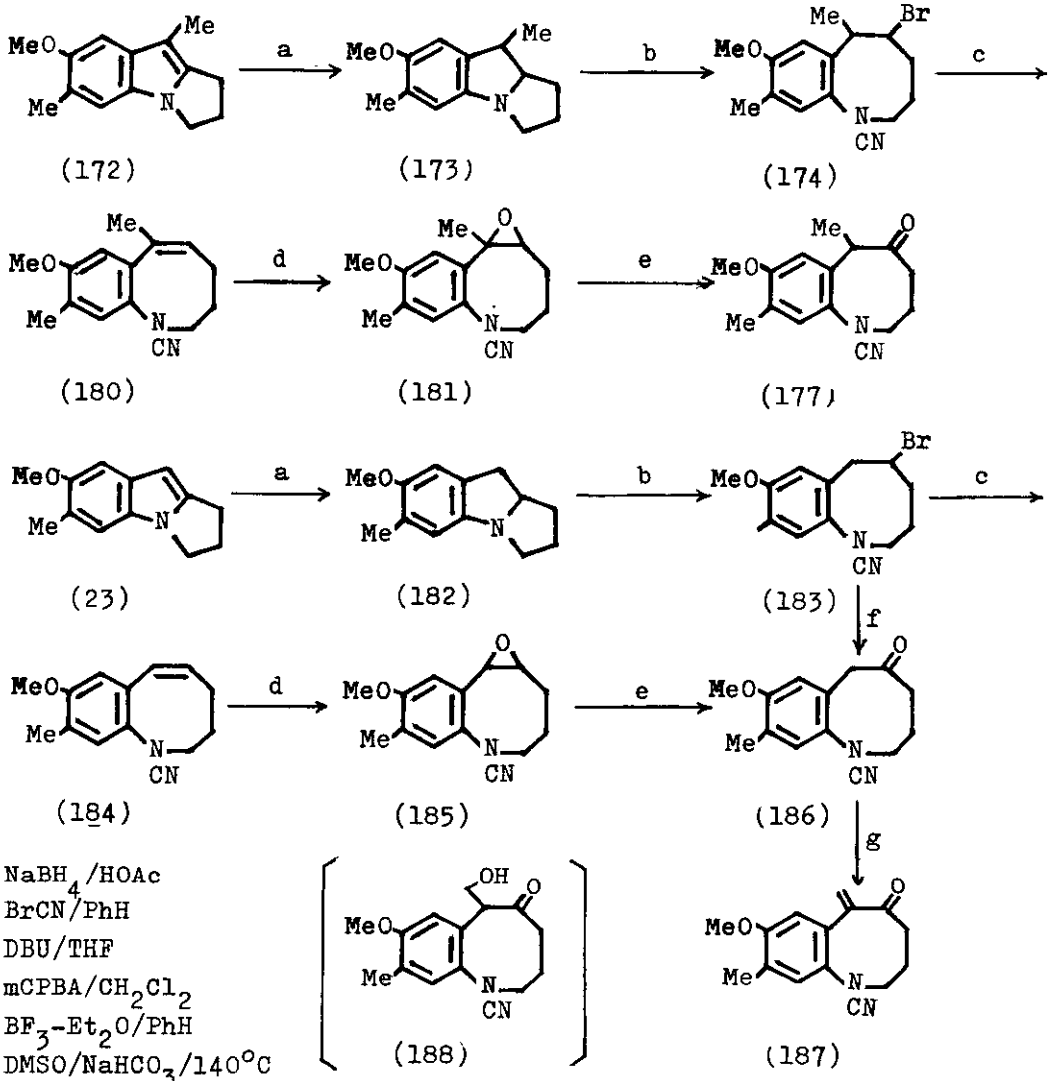


a. $NaBH_4$/MeOH
b. NH_2NH_2/NaOH/diethylene glycol
c. $NaBH_4$/HOAc
d. MnO_2/CH_2Cl_2
e. BrCN/PhH
f. DMSO/$NaHCO_3$

by oxidation with dimethyl sulphoxide in the presence of sodium hydrogen carbonate.[99] Thus, the bromide (174) afforded the ketone (177) whereas the bromide (178) gave the aldehyde (179).

Although the conversion of the pyrrolo[1,2-a]indole into the required 1-benzazocin-5-one (177) was achived, there were problems with this route: namely, the formation of a complex mixture in the reduction of the aldehyde (24) and the low yield in the oxidation of the bromide (174) to the ketone (177), therefore alternative synthesis of (177) was examined. The product (172) obtained by Wolff Kishner reduction of (24) was reduced to the indoline (173), with sodium borohydride in acetic acid, in high yield. Treatment of (173) with cyanogen bromide in benzene selectively cleaved the 4-9a bond to furnish the benzazocine derivative (174). Dehydrobromination of (174), by heating with DBU in tetrahydrofuran, yielded the olefin (180), which on stirring with m-chloroperbenzonic acid in dichloromethane gave the epoxide (181). Treatment of (181) with boron trifluoride ether in benzene at room temperature for 5 min provided the ketone (177). Similar treatment of the pyrrolo[1,2-a]indole (23), prepared by the reported procedure,[31] gave the desired ketone (186). Reaction of the ketone (186) with paraformaldehyde in the presence of sodium hydride gave the methylene compound (187) but the expected alcohol (188) was not obtained. The ketones (172 and 186) were quantitatively converted into the pyrrolo[1,2-a]indoles (177 and 23) by transannular cyclisation upon refluxing in ethanolic sulphric acid. Thus at this stage, the interconversion of the pyrrolo[1,2-a]indole and 1-benzazocin-5-one systems was establised. (Chart 32)

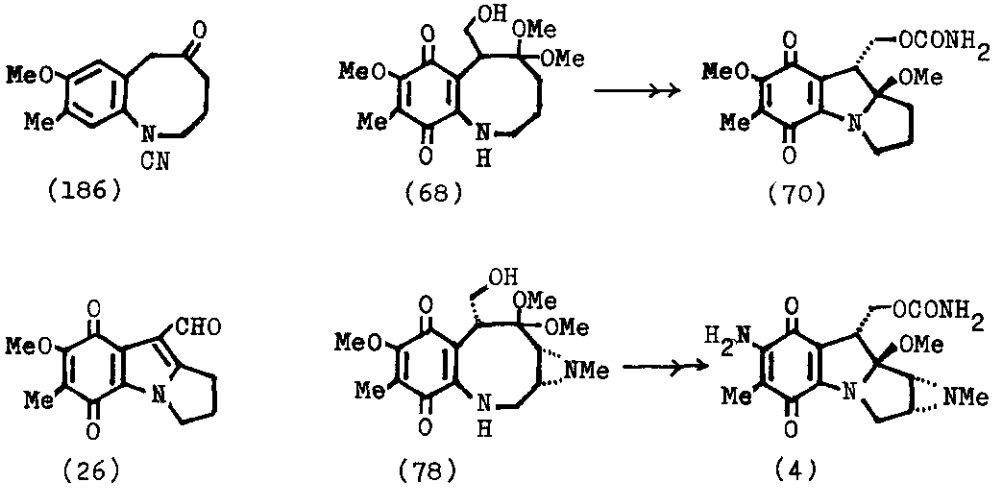
Chart 32


(172)
(173)
(174)
(180)
(181)
(177)
(23)
(182)
(183)
(184)
(185)
(186)
(188)
(187)
a. $NaBH_4$/HOAc
b. BrCN/PhH
c. DBU/THF
d. mCPBA/CH_2Cl_2
e. BF_3-Et_2O/PhH
f. DMSO/$NaHCO_3$/140°C
g. HCHO/NaH/THF/-20°C

Part 2 Synthesis of seco-Mitosane Type compounds

In the total synthesis of mitomycins,[52-54] seco-mitosane type compounds, namely compounds with eight-membered ring fused to a quinone ring, e.g. (68) and (78), were important synthetic precursors. Elaboration of the quinone from the 1-benzazocin-5-one (186), which was described in Part 1, or conversion of the indolo-quinone (26) into a 1-benzazocin-5-one, may enable the synthesis of seco-mitosanes (68 and 78).

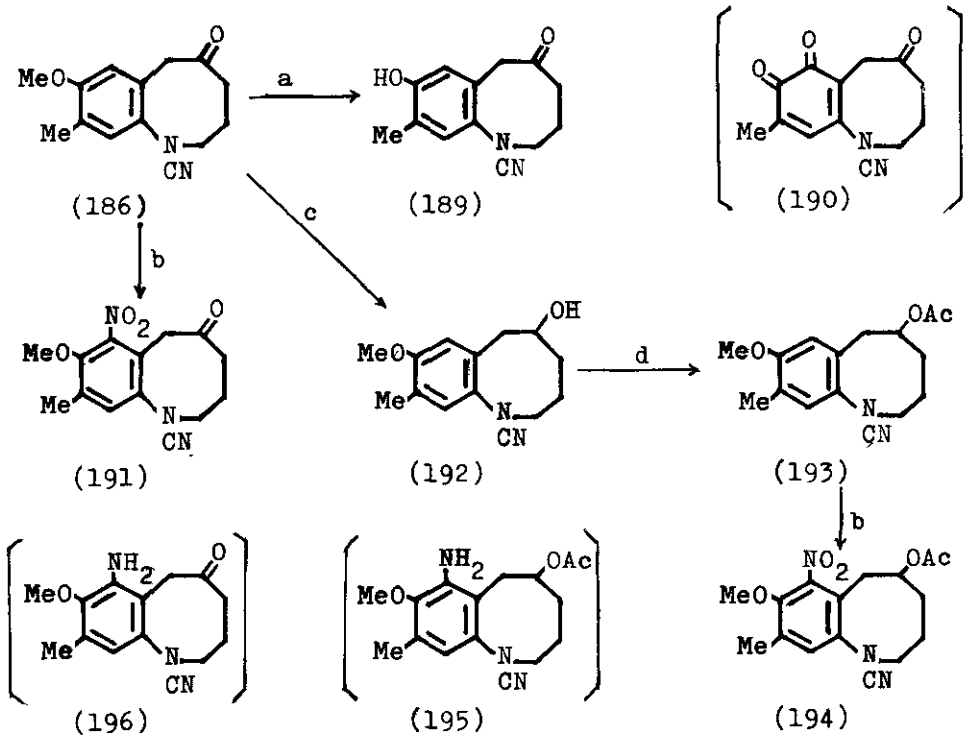
Chart 33



Firstly, the introduction of quinone functions into 1-cyano-1-benzazocine derivatives was examined. Namely, oxidation of the phenolic compound (189), prepared by ether cleavage of (186) using boron tribromide, with Fremy's salt was attempted but gave none of the desired o-quinone (190), with only starting material being recovered. Then reduction of the nitro compounds (191 and 194) was attempted. 1-Cyano-1,3,4,6-tetrahydro-7-nitro-1-benzazocin-5(2H)- one (191) was prepared from (186) by treatment with nitric acid. 5-Acetoxy-1-cyano-1,2,3,4,5,6-hexahydro-7-nitro-1-benzazocine (194) was prepared as follows. Sodium borohydride reduction of the ketone (186) gave (192), the acetylation of which, followed by

nitration of the resulting acetate (193), afforded (194). Reduction of the nitro compounds (191 and 194) gave none of the desired 7-amino derivatives with only complex mixtures being obtained.

Chart 34

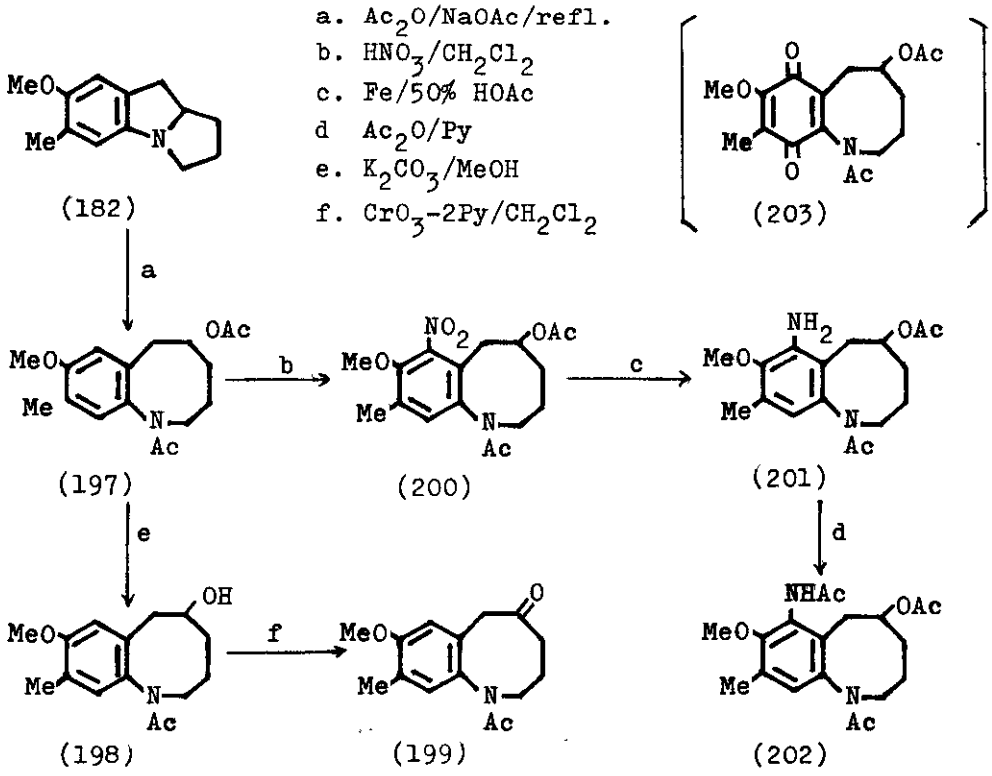


a. $BBr_3/CH_2Cl_2/-20°C$
b. HNO_3/CH_2Cl_2
c. $NaBH_4/MeOH$
d. Ac_2O/Py

Secondly, transformation of the 1-acetyl-1-benzazocine derivatives, prepared as follows, was examined. Heating the indoline (182) with acetic anhydride and sodium acetate[100,101] yielded the 5-acetoxy-1-acetyl-1,2,3,4,5,6-hexahydro-1-benzazocine (197). Hydrolysis of the O-acetyl group of (197) with potassium carbonate in aqueous methanol afforded the alcohol

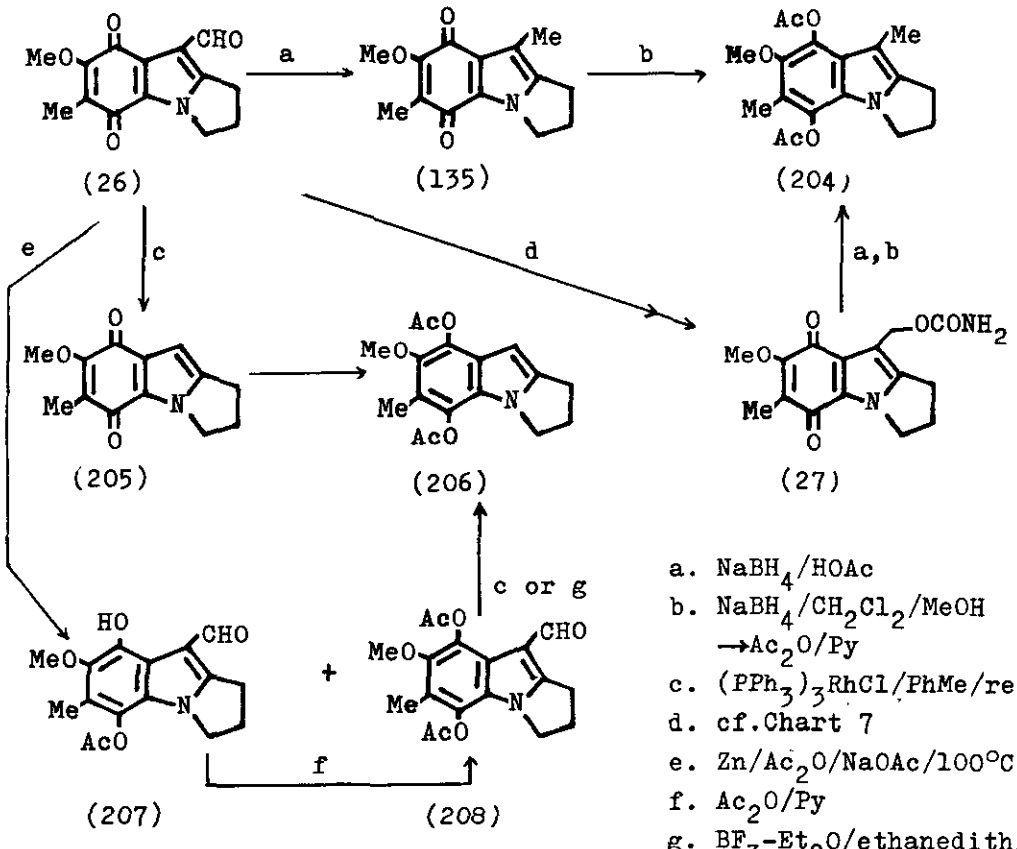
(198). The n.m.r. spectra of (197 and 198) (see Experimental Section) indicated the presence of two rotamers[102] about the amide linkage, in a ratio of ca 1:1. Oxidation of the alcohol (198) was carried out with the chromium trioxide-pyridine complex in dichloromethane at room temperature, to give the 1-benzazocin-5(2H)-one (199). Although 5-acetoxy-1-acetyl-7-amino-1,2,3,4,5,6-hexahydro-1-benzazocine (201) could be prepared in good yield from (197) by nitration, followed by reduction of the resulting nitro compound (200), oxidation of the amine derivative (201) with Fremy's salt failed to give the quinone compound (203).

Chart 35



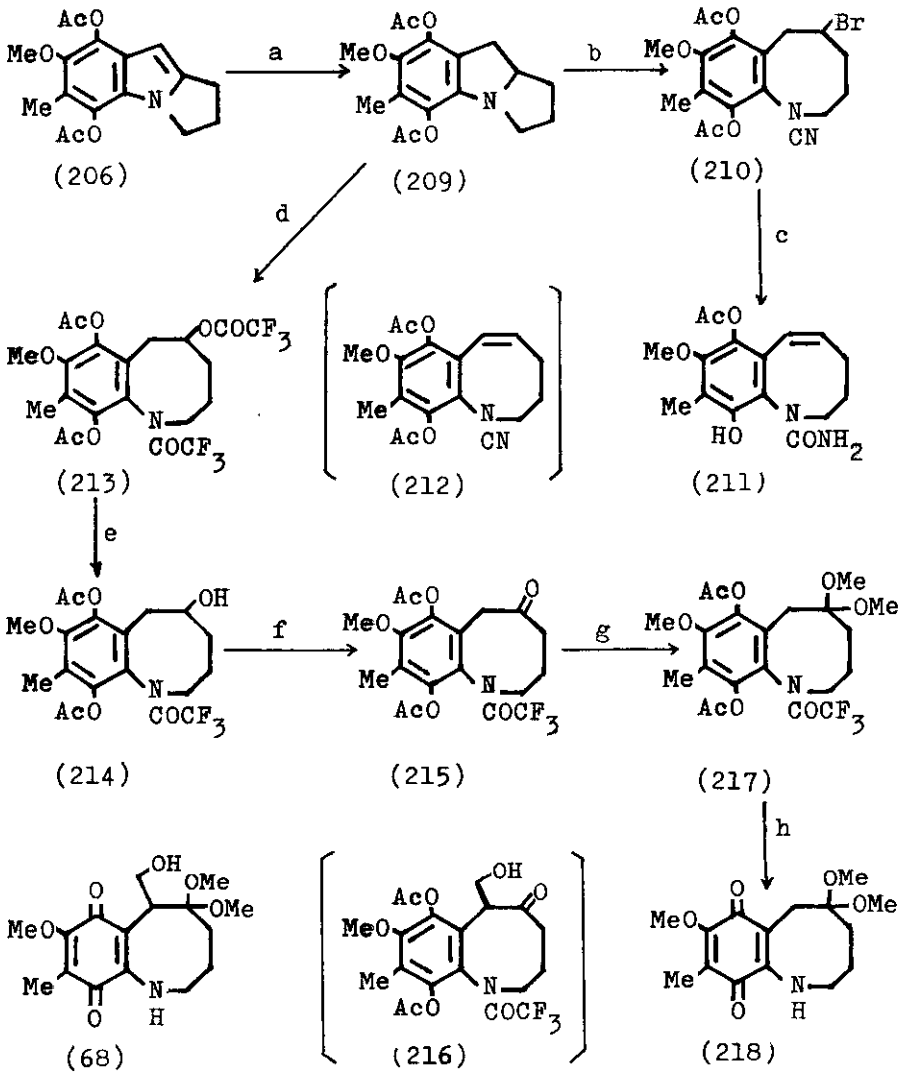
Finally, synthesis of the quinone fused with the eight-membered ring was achieved by the conversion of the indoloquinone (26) into 7,10-diacetoxy-1-trifluoroacetyl-5,5,8-trimethoxy-1-benzazocine (217) followed by removal of the protecting groups. Transformation of the indoloquinone (26) into the 5,8-diacetoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indoles (204 and 206) was accomplished as follows. Reduction of the indoloquinone (135), prepared from (26) as described previously, with sodium borohydride in dichloromethane containing a small amount of methanol, followed by ready acetylation under nitrogen to give the diacetate (204). 7-Methoxymitosene also afforded (204) in a similar manner. The acetate (206) was obtained from (205), prepared from the aldehyde (26) by decarbo-

Chart 36



nylation[103] of the 9-formyl group with tris(triphenylphosphine)chlororhodium, in a similar manner. The acetate (206) was also obtained as follows. Treatment of the quinone (26) with zinc dust in acetic anhydride, in the presence of sodium acetate,[104] afforded a mixture of the monoacetate (207) and the diacetate (208) in a ratio of ca. 1:1. The phenolic compound (207)[105] could be easily converted into (208) with acetic anhydride and pyridine. Decarbonylation of (208) with tris(triphenylphosphine)chlororhodium, or by the reaction[106] of (208) with boron trifluoride etherate in ethanedithiol, afforded (206). Although sodium borohydride reduction of (206) in acetic acid had given the indoline (209) in low yield, catalytic hydrogenation of (206) in the presence of platinum and tetrafluoroboric acid[107] afforded (209) almost quantitatively. A von Braun reaction of the indoline (209) gave 5-bromo-1-cyano-1-benzazocine (210). On treatment of (210) with DBU in tetrahydrofuran, 1-aminocarbonyl-1,2,3,4-tetrahydro-10-hydroxy-1-benzazocine (211) was obtained in low yield,[108] rather than the desired (212). At this stage, the author selected an alternative route to the benzazocine from the indoline (209). Thus, heating the indoline (209) with trifluoroacetic anhydride[109] in a sealed tube at 150-160°C for 1.5 h afforded the ring cleaved compound (213) in good yield. Selective hydrolysis of the O-trifluoroacetyl group in a solution of sodium hydrogen carbonate in aqueous methanol afforded the alcohol (214). On treatment of the alcohol (214) with the chromium trioxide-pyridine complex in dichloromethane, the ketone (215) was obtained. Acetalisation of (215) was achieved with trimethyl orthoformate in methanol in the presence of boron trifluoride-etherate to give the acetal (217). Hydroxymethylation of the ketone (215) under similar conditions as before gave, not the alcohol (216), but an unclarified mixture. Removal of the two kinds of acyl groups from (217), to give the quinone (218), was accomplished by treatment of (217) with lithium aluminium hydride in tetrahydrofuran at room temperature, followed by air

Chart 37



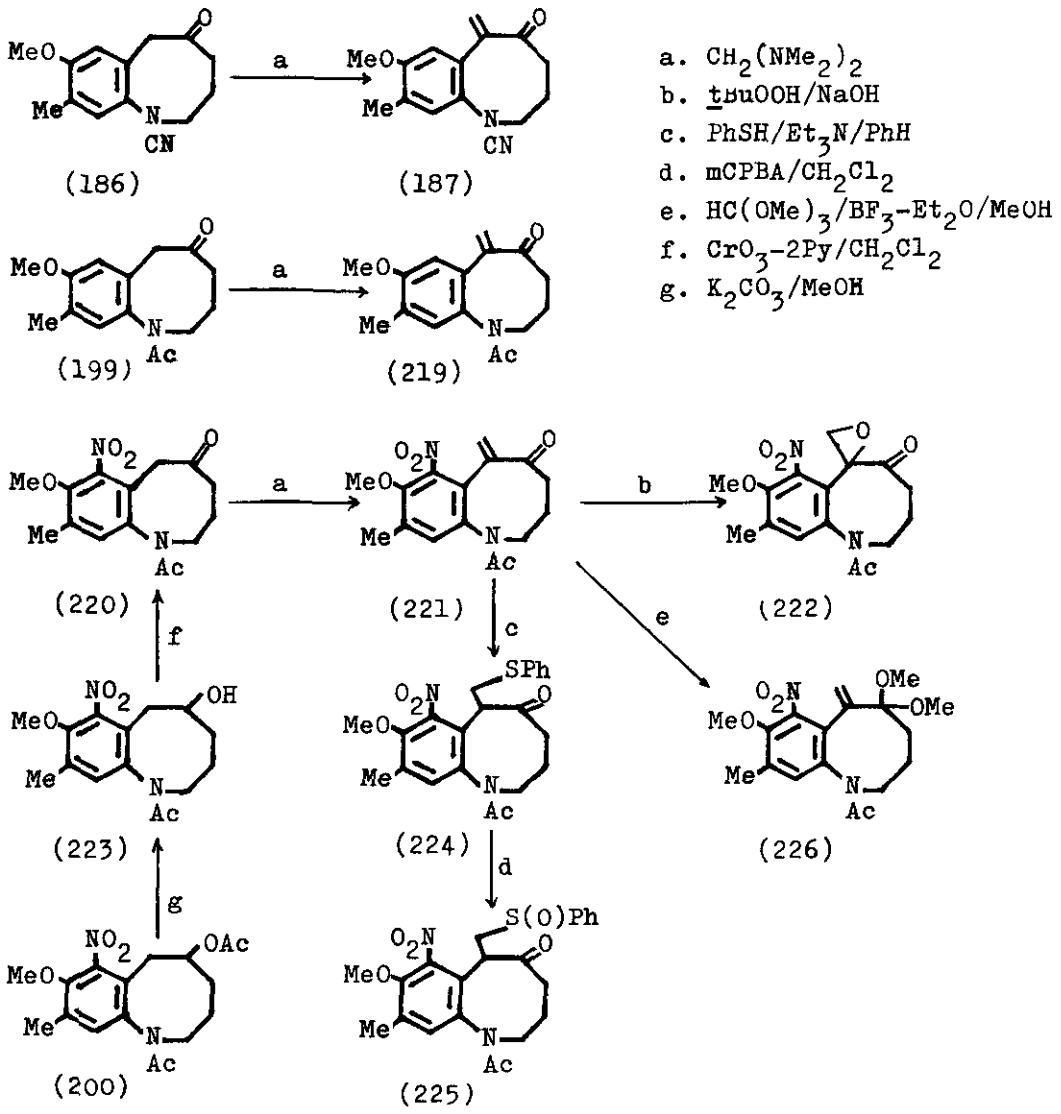
a. $H_2/HBF_4/Pt$
b. BrCN/PhH
c. DBU/THF
d. $(CF_3CO)_2O/160^oC$
e. $NaHCO_3$/MeOH
f. CrO_3-2Py/CH_2Cl_2
g. $HC(OMe)_3/BF_3$-Et_2O/MeOH
h. LAH/THF

oxidation of the crude product. Thus, transformation of the indoloquinone (26), a precursor of 7-methoxymitosene (27), into the so-called "eight-membered quinone" has been completed. Furthermore, it was found that transannular cyclisation of (218) with tetrafluoroboric acid[55] in dichloromethane yielded (206).(Chart 37).

As hydroxymethylation of the ketone (215) was not successful and, as described in the previous part, the same reaction of the ketone (186) did not yield (188), but the methylene compound (187), introduction of the C-one unit in the 6-position of 1-benzazocin-5-ones was examined. Treatment of (186) with bis(dimethylamino)methane[110,111] and acetic anhydride afforded the methylene compound (187). The physical data for this compound (187) were identical to those for the one obtained by hydroxymethylation. Similarly, the ketone (199) afforded (219), and the ketone (220), obtained from (200) by hydrolysis followed by oxidation of the resulting alcohol, yielded (221). The enone (221) was treated with sodium hydroxide and t-butyl hydroperoxide to give the epoxide (222). Furthermore, 1,4-addition of thiophenol afforded the adduct (224). Oxidation of (224) with m-chloroperbenzoic acid gave the S-oxide (225), which was re-converted to the enone (221) on heating in acetic anhydride at 100°C. The enone (221) afforded the acetal (226) on treatment with trimethylorthoformate and boron trifluoride-etherate in methanol. (Chart 38).

Similar reactions were carried out on the compound (215). On treatment with bis(dimethylamino)methane and acetic anhydride, the ketone (215) afforded the enone (227), which was acetalised to give (228). Although the enone (227) could not be transformed into the epoxide (232) because of its instability towards the basic conditions, (227) yielded the 1,4-adduct (229) on treatment with thiophenol. Reduction of (227) and (228) with lithium aluminium hydride in tetrahydrofuran, followed by air oxidation furnished the quinones (230 and 231), respectively. The quinone

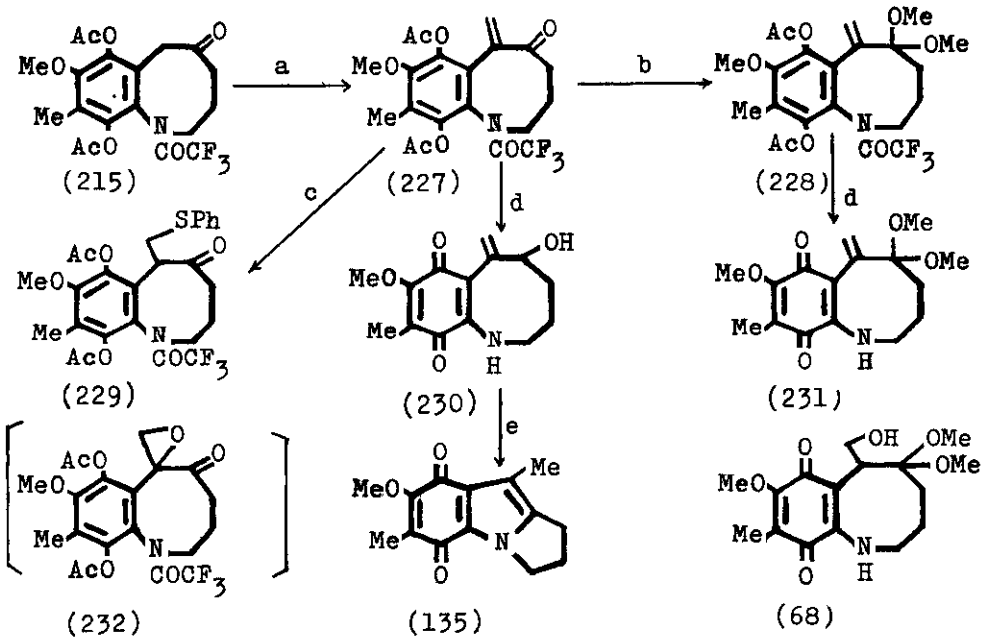
Chart 38



(230) afforded the indoloquinone (135) by transannular cyclisation, followed by dehydration when it was treated with hydrochloric acid.[112] As described above, although the synthesis of the expected compound (68) has not yet been accomplished, the synthetic pathway of the seco-mitosane type compounds from the mitosene type compounds has been established.

This fact seems to be significant because it will enable a connection to be made between the traditional extensive studies on mitomycins and the total synthesis procedure according to the biosynthetic pathway.

Chart 39



a. $CH_2(NMe_2)_2/Ac_2O$
b. $HC(OMe)_3/BF_3$-Et_2O/MeOH
c. $PhSH/Et_3N$/PhH
d. LAH/THF
e. HCl/Me_2CO

CONCLUSION

First of all, the facile synthesis of the 2,3-dihydro-1H-pyrrolo[1,2-a]indole system, the fundamental skeleton of the mitomycins, has been achieved. Namely, condensation of 2-bromo-5-methoxy-4-methylphenylacetonitrile (85) with 2-methoxy-Δ^1-pyrroline (86) in the presence of DBU afforded the Z-α-(2-bromo-5-methoxy-4-methylphenyl)-α-pyrrolidin 2-ylideneacetonitrile (84), which gave 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carbonitrile (107) on treatment with sodium hydride and copper (I) bromide in dimethylformamide. The nitrile (107) was converted to 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (24) by the reaction with nickel-aluminium alloy in aqueous acetic acid. This aldehyde was transformed to 2,3-dihydro-7-methoxy-6-methyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole-9-carbaldehyde(26), by nitration of (24), followed by reduction of the nitro compound and oxidation of the resulting amine with Fremy's salt. 7-Methoxy-mitosene (27) was synthesized from (26) by a reported procedure.

Secondly, introduction of functional group into the 2,3-dihydro-1H-pyrrolo[1,2-a]indole system was examined. Reaction of (107) with NBS in methanol gave a 1:1 mixture of 5-bromo2,3-dihydro-7,8-dimethoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carbonitrile (123) and 5-bromo-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carbonitrile (122). Similar treatment of 2,3-dihydro-1H-pyrrolo[1,2-a]indole-5,8-diones afforded the adducts in which the methoxyl group was introduced at the 7-position rather than at the 9a-position. 2,3-Dihydro-1H-pyrrolo[1,2-a]indoles (24, 59 and 107) were acetoxylated at the 1-position on treatment with lead tetraacetate in acetic acid. Elimination of acetic acid from methyl 1-acetoxy-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carboxylate (159) gave methyl 7-methoxy-6-methyl-3H-pyrrolo[1,2-a]indole-9-carboxylate (37), from which Matsui had prepared the tetracyclic aziridino compound (39). Syntheses of 1-acetoxy-7-methoxymitosene (30) and desammono-apo-mitomycin A (12) were accomplished from 1-acetoxy-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo-

[1,2-a]indole-9-carbaldehyde (152) according to Remer's procedure.

Finally, synthesis of seco-mitpsane type compounds was attempted in order to be able to introduce the 9a-methoxyl group, which seemed to be the most difficult problem in synthetic studies on mitomycins. 2,3-Dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole (23) was reduced with sodium borohydride in acetic acid to give the 2,3,9,9a-tetrahydro-compound (182), which was cleaved by cyanogen bromide to afford 5-bromo-1-cyano-1,2,3,4,5,6-hexahydro-7-methoxy-6-methyl-1-benzazocine (183). This bromide (183) was transformed to 1-cyano-1,3,4,6-tetrahydro-8-methoxy-9-methyl-6-methylene-1-benzazocin-5(2H)-one (186), but attempted introduction of the quinone group resulted in failure. Synthesis of the so-called "eight-membered quinone" was accomplised from the 5,8-diacetoxy-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole (206). Thus, (206) was reduced to the 2,3,9,9a-tetrahydro derivative (209) by catalytic hydrogenation in the presence of platinum oxide and tetrafluoroboric acid. Heating the indoline (209) with trifluoroacetic anhydride afforded the ring-opened product (213). Hydrolysis of 7,10-diacetoxy-5-trifluoroacetoxy-1-trifluoroacetyl-1,2,3,4,5,6-hexahydro-8-methoxy-9-methyl-1-benzazocine (213), followed by oxidation of the resulting alcohol (214) afforded 7,10-diacetoxy-1-trifluoroacetyl-1,3,4,6-tetrahydro-8-methoxy-9-methyl-1-benzazocin-5(2H)-one (215). Although hydroxymethylation of the ketone (215) failed, a methylene function could be introduced at the 6-position to give (227). Removal of the protecting group afforded the quinone (218, 230 and 231). This conversion seemed to be significant because it connected the synthetic intermediate of mitosene to the seco-mitosane type compound.

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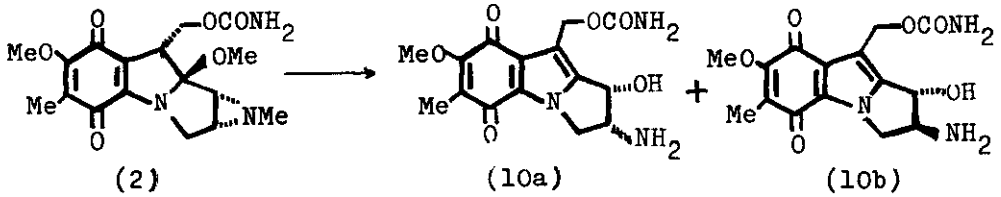

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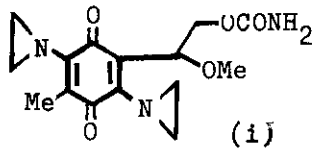

(i)

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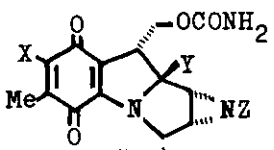
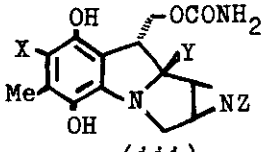
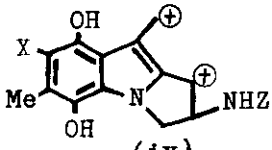


(ii)



(iii)



(iv)

Substituent group X effects reduction-oxidation potential, Y relates to formation of indole ring, and Z participates in the protonation which cleaves the aziridine ring. Aziridinomitosene is also thought to form (iv).

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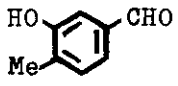
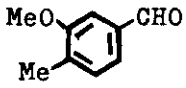
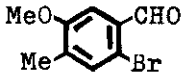


(101)



(101a)



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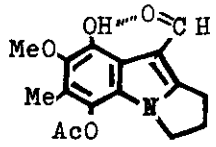

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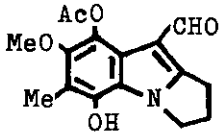

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