SYNTHESIS OF SECO-MITOSANE TYPE COMPOUNDS AS KEY INTERMEDIATES TO MITOMYCINS

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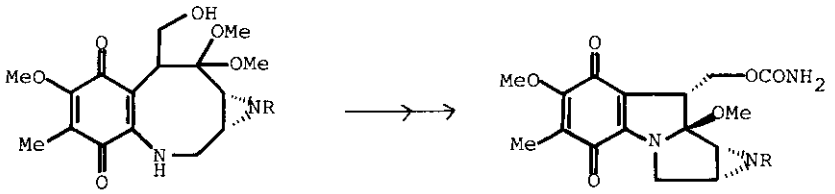
Abstract — 1,3,4,6-tetrahydro-6-methylene-1-benzazocin-5(2H)-ones (4 and 13) were prepared from 1,3,4,6-tetrahydro-1-benzazocin-5(2H)-ones (3 and 12) by treatment with N,N,N',N'-tetramethyldiaminomethane and acetic anhydride. Functionallisation of the methylene groups of (4 and 13) and transannular cyclisation of the seco-mitosane type compounds (16 and 17) are also described.

In the total synthesis of mitomycins (2)[1], the only successful route known to date involves transannular cyclisation of the so-called "eight-membered quinone" (1) — a "seco-mitosane" type compound. In earlier papers we reported the interconversion of pyrrolo[1,2-a]indoles and 1-benzazocin-5-ones, e.g. (3a)[2], and the synthesis of "seco-mitosane" type compound (17a)[3]. In this article we describe the synthesis and transannular cyclisation of 8-membered ring compounds.

Chart 1

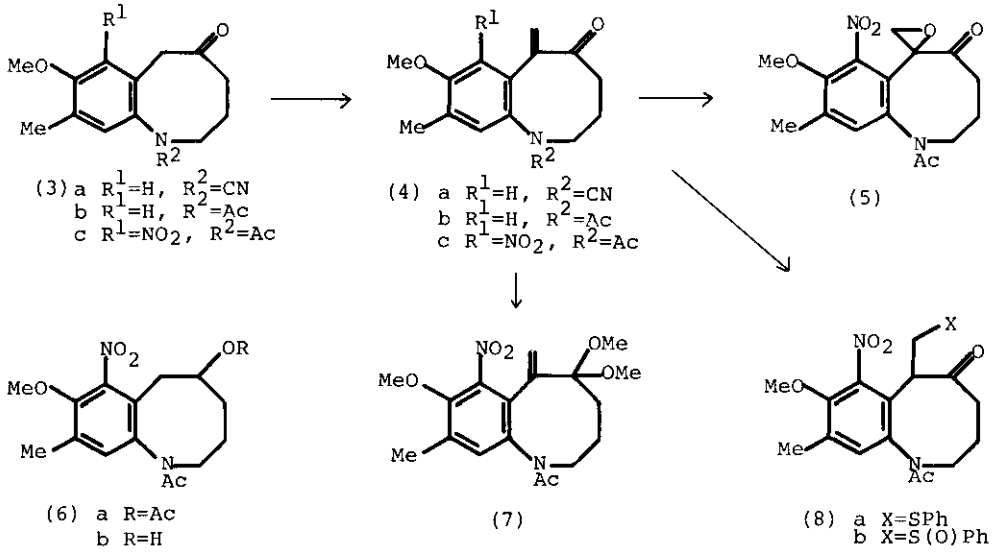


(1) R=Me
R=$(CH_2)_3OAc$

(2) R=Me
R=H

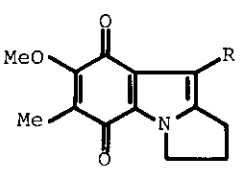
As previously described, attempted hydroxymethylation of the ketone (12) failed to yield the alcohol (15a) but gave an unclarified mixture[3], while the same treatment of ketone (3a) afforded the methylene compound (4a) in low yield[2]. As a result of this small degree of success with the latter compound, the introduction of a one-carbon unit into ketone (3) was investigated. The ketone (3a), on treatment with N,N,N',N'-tetramethyldiaminomethane[4,5] and acetic anhydride, afforded the enone (4a) in excellent yield. Under the same conditions ketones (3b) and (3c) [the latter prepared from the acetate (6a) by hydrolysis and oxidation of the resulting alcohol (6b)] afforded the enones (4b) and (4c), respectively. Treatment of (4c) with trimethyl orthoformate in methanol, in the presence of boron trifluoride diethyl ether, afforded the acetal (7). Subsequently, functionallisation of the methylene group in such compounds was examined. Thus, reaction of the enone (4c) with alkaline hydroperoxide gave the epoxide (5). Also, enone (4c) gave the sulphide (8a) on treatment with thiophenol in the presence of triethylamine in benzene. Oxidation of this sulphide (8a) with m-chloroperbenzoic acid in dichloromethane afforded the sulphoxide (8b). Although no reaction occurred on treatment of the sulphoxide (8b) with trifluoroacetic anhydride or acetic anhydride at low temperature, the original enone (4c) was obtained on heating with the latter reagent at 100°C.

Chart 2

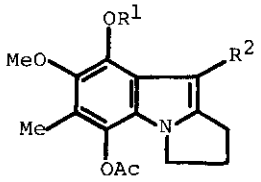


On the basis of the above results, introduction of a one-carbon unit into a derivative, i.e. (12), which could be converted to the "seco-mitosane" type compound was examined. In a previous paper, we reported the synthesis of (12) via ring cleavage of the indoline (11) [prepared by catalytic hydrogenation of (10c)] effected by treatment with trifluoroacetic anhydride. The resulting trifluoroacetate was converted to the ketone (12) by successive hydrolysis and oxidation. The compound (10c) had been prepared from the quinone (9c) by reduction and acetylation[3]. An alternative route to (10c) is described here. Thus, reductive acetylation of the quinone (9a), by treatment with zinc dust and acetic anhydride, afforded a mixture of mono-acetate (10a)[6] and di-acetate (10b) in a ratio of ca 1 : 1. The mono-acetate (10a) was readily converted to (10b) in acetic anhydride and pyridine. The di-acetate (10b) was decarbonylated on treatment with tris(triphenylphosphine)chlororhodium, or with boron trifluoride diethyl ether in ethanedithiol[7], to afford the indole (10c). The ketone (12), obtained from (10c) as already described, was converted into the enone (13) by treatment with N,N,N',N'-tetramethyldiaminomethane and acetic anhydride as described above for the conversion of (3) to (4). In analogy with the reaction of enone (4c), enone (13) underwent acetalisation to afford (14) and added thiophenol to give the sulphide (15b). However, epoxidation of (13) failed because of the instability of the enone (13) towards the basic conditions. Removal of the two types of acetyl groups of (13) and (14) by treatment with lithium aluminium hydride gave the quinones (16) and (17b), respectively. Although attempted transannular cyclisation of the acetal (17b) gave a complex mixture, the alcohol (16) afforded the indoloquinone (9b) on treatment with hydrochloric acid[8].

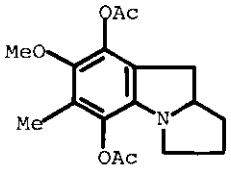
Chart 3



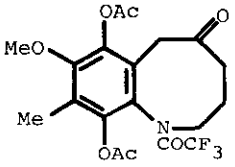
(9) a R=CHO
b R=Me
c R=H



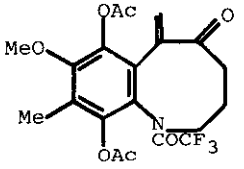
(10) a R=H R^2=CHO
b R=Ac R^2=CHO
c R^1=Ac R^2=H



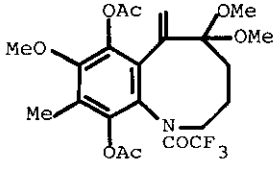
(11)



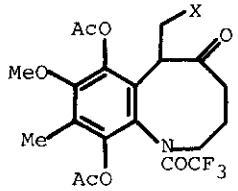
(12)



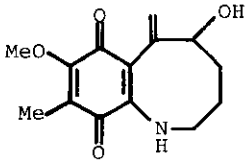
(13)



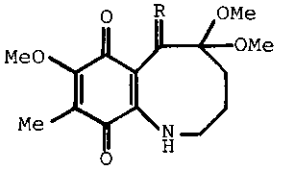
(14)



(15) a X=OH
b X=SPh



(16)



(17) a R=H_2
b R=CH_2

EXPERIMENTAL SECTION

All m.p.s are uncorrected and were taken with a Yanagimoto Micro apparatus (MP-S2). I.r. spectra were measured with a Hitachi 215 recording spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX 60 spectrophotometer, and mass spectra with a Hitachi M-52G spectrometer.

1-Acetyl-1,2,3,4,5,6-hexahydro-5-hydroxy-8-methoxy-9-methyl-6-nitro-1-benzazocine (6b). ——— A mixture of the acetate (6a) (500mg), potassium carbonate (200 mg), water (1 ml), and methanol (20 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated to leave (6b) (365 mg, 83 %) as prisms (from diethyl ether), m.p. 148 - 149°C (Found: C, 58.10; H, 6.43; N, 9.93. $C_{15}H_{20}N_2O_5$ requires C, 58.43; H, 6.54; N, 9.09 %), $\nu_{max.}$ ($CHCl_3$) 1650 cm^{-1} (>N.CO); δ($CDCl_3$) 1.80 (3H, s, Ac), 2.38 (3H, s, 9-Me), 3.80 (3H, s, OMe), and 7.24 (1H, s, ArH); m/e 308 (M^+).

1-Acetyl-1,3,4,6-tetrahydro-8-methoxy-9-methyl-7-nitro-1-benzazocin-5(2H)-one (3c). ——— To a solution of chromium trioxide-pyridine complex [prepared from chromium trioxide (1.0 g)] in dichloromethane (20 ml) was added the alcohol (6b) (450 mg) in dichloromethane (10 ml), and the resulting mixture was stirred at room temperature for 10 min. The mixture was washed with 5 % aqueous hydrochloric acid and aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with chloroform as eluent to yield (3c) (385 mg, 86 %) as prisms, m.p. 118 - 119°C (from n-hexane-diethyl ether) (Found: 58.63; H, 5.86; N, 8.95. $C_{15}H_{18}N_2O_5$ requires C, 58.81; H, 5.92; N, 9.15 %), $\nu_{max.}$ ($CHCl_3$) 1710 (C=O) and 1670 cm^{-1} (N.CO); δ(CCl_4) 1.72 (3H, s, Ac), 2.46 (3H, s, 9-Me), 3.54 (2H, s, $ArCH_2CO$), 4.00 (3H, s, OMe) and 7.34 (1H, s, ArH); m/e 306 (M^+).

1-Cyano-1,3,4,6-tetrahydro-8-methoxy-9-methyl-6-methylene-1-benzazocin-5(2H)-one (4a). ——— A mixture of the ketone (3a) (120 mg), N,N,N',N'-tetramethyldiaminomethane (0.5 ml), and acetic anhydride (0.5 ml) was stirred at room temperature for 15 h under nitrogen. The volatile matter was evaporated under reduced pressure, and the residue was chromatographed on silica gel. Elution with dichloromethane gave a solid, recrystallisation of which from diethyl ether afforded (4a) (108 mg, 86 %) as needles, m.p. 147 - 148° (lit.,[2] 147 - 148°), identicl (i.r. and n.m.r. spectra) to that reported.

1-Acetyl-1,3,4,6-tetrahydro-8-methoxy-9-methyl-6-methylene-1-benzazocin-5(2H)-one (4b). ——— Under the same coditions as above, the ketone (3b) (260 mg) afforded (4b) (236 mg, 86 %) as an oil, $\nu_{max.}$ ($CHCl_3$) 1690 (C=O) and 1650 cm^{-1} (>N-CO); δ ($CDCl_3$) 1.64 (3H, s, Ac), 2.30 (3H, s, 9 - Me), 3.94 (3H, s, OMe), 5.76 and 6.30 (each 1H, each d, J 2 Hz, 2 x olefinic H), and 7.00 and 7.06 (each 1H, each s, 2 x ArH); m/e 273 (M^+).

1-Acetyl-1,3,4,6-tetrahydro-8-methoxy-9-methyl-6-methylene-7-nitro-1-benzazocin-5-(2H)-one (4c). ——— Under the same conditions as above, the ketone (3c) (300 mg) afforded (4c) (252 mg, 81 %) as prisms, m.p. 152 - 153° (Found: C, 60.53; H, 5.86; N, 8.71. $C_{16}H_{18}N_2O_5$ requires C, 60.37; H, 5.70; N, 8.80 %), $\nu_{max.}$ ($CHCl_3$) 1690 (C=O), 1660 cm^{-1} (>N-CO); δ ($CDCl_3$) 1.68 (3H, s, Ac), 2.44 (3H, s, 9 - Me), 3.96 (3H, s, OMe), 5.76 and 6.50 (each 1H, each s, 2 x olefinic H), and 7.96 (1H, s, ArH); m/e 318 (M^+).

7,8-Diacetoxy-1-trifluoroacetyl-1,3,4,6-tetrahydro-8-methoxy-9-methyl-6-methylene-1-benzazocin-5(2H)-one (13). ——— Under the same conditions as above, the ketone (12) (430 mg) gave (13) (366 mg, 83 %) as a syrup. $\nu_{max.}$ ($CHCl_3$) 1770 (OAc), 1700 cm^{-1} (>N-$COCF_3$ and C=O); δ (CCl_4) 2.12, 2.20 and 2.28 (each 3H, each s, 2 x Ac and 9 - Me), 3.84 (3H, s, OMe), and 5.56 and 6.46 (each 1H, each d, J 2 Hz, 2 x olefinic H); m/e 443 (M^+).

Epoxidation of 1-acetyl-1,3,4,6-tetrahydro-8-methoxy-9-methyl-6-methylene-7-nitro-1-benzazocin-5(2H)one (4c). ——— To a solution of the enone (4c) (20 mg) and 70 % tert. butyl hydroperoxide (40 mg) in methanol (4 ml) was added sodium hydroxide (2 mg) in water (0.5 ml). The solution was stirred at -15°C for 20 min under nitrogen. The mixture was poured into water, extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated to leave a solid, recrystallisation of which from ethanol-diethyl ether afforded the epoxide (5) (19 mg, 87 %) as prisms, m.p. 141 - 142°C (Found: C, 57.24; H, 5.47; N, 8.41. $C_{16}H_{18}N_2O_6$ requires C, 57.48; H, 5.43; N. 8.38 %), $\nu_{max.}$ ($CHCl_3$) 1720 (C=O) and 1665 cm^{-1} (N.Ac); δ ($CDCl_3$) 1.84 (3H, s, Ac), 2.44 (3H, s, 9 - Me), 3.82 (3H, s, OMe), and 7.28 (1H, s, ArH); m/e 334 (M^+).

1-Acetyl-1,2,3,4,5,6-hexahydro-5,5,8-trimethoxy-9-methyl-6-methylene-7-nitro-1-benzazocine (7). ——— A mixture of the ketone (4c) (32 mg), trimethyl orthoformate (0.1 ml), methanol (2 ml) and boron trifluoride-diethyl ether (1 drop) was stirred at room temperature for 15 h. The reaction mixture was poured into aqueous sodium hydrogen carbonate solution. The resulting mixture was extracted with di-

chloromethane. The organic extract was dried and evaporated to afford the acetal (7) (33 mg, 90 %) as a viscous syrup, $\nu_{max.}$ ($CHCl_3$) 1660 cm^{-1} (Ac); 1.80 (3H, s, Ac) 2.42 (3H, s, 9 - Me), 3.02 and 3.18 (each 3H, each s, 2 x 5 - OMe), 3.94 (3H, s, 8-OMe), 5.36 and 5.84 (each 1H, each s, 2 x olefinic H), and 7.18 (1H, s, 10 - H); m/e 364 (M^+).

7,10-Diacetoxy-1-trifluoroacetyl-1,2,3,4,5,6-hexahydro-5,5,8-trimethoxy-9-methyl-6-methylene-1-benzazocine (14). ——— A mixture of the ketone (227) (44 mg), trimethyl orthoformate (0.1 ml), methanol (2 ml) and boron trifluoride-diethyl ether (2 drops) was stirred at room temperature for 15 h. Work up as above afforded the acetal (13) (45 mg, 93 %) as a viscous syrup, $\nu_{max.}$ ($CHCl_3$) 1760 (OAc) and 1695 cm^{-1} ($N.COCF_3$); δ (CCl_4) 2.06, 2.14 and 2.20 (each 3H, each s, 2 x Ac and 9 - Me), 3.04 and 3.20 (each 3H, each s, 2 x 5 - OMe), 3.78 (3H, s, 8 - OMe), and 5.18 and 5.72 (each 1H, each d, J 2 Hz, 2 x olefinic H); m/e 489 (M^+).

1-Acetyl-1,3,4,6-tetrahydro-8-methoxy-9-methyl-7-nitro-6-phenylthiomethyl-1-benzazocin-5(2H)one. ——— A mixture of the enone (4c) (30 mg), thiophenol (15 mg), triethylamine (30 mg), and benzene (1 ml) was refluxed in a current of nitrogen for 24 h. The mixture was evaporated and the residue was chromatographed on silica gel. Elution with chloroform-methanol (98 : 2 v/v) afforded (8a) (38 mg, 94 %) as a syrup $\nu_{max.}$ ($CHCl_3$) 1710 (C=O) and 1670 cm^{-1} (>N.CO); δ (CCl_4) 1.84 (3H, s, Ac), 2.44 (3H, s, 9 - Me), 3.90 (3H, s, OMe), 7.20 (1H, s, 10 - H), and 7.30 - 7.80 (5H, m, 5 x ArH); m/e 428 (M^+).

7,10-Diacetoxy-1-trifluoroacetyl-1,3,4,6-tetrahydro-8-methoxy-9-methyl-6-phenylthiomethyl-1-benzazocin-5(2H)one (15b). ——— A mixture of the enone (13) (443 mg), thiophenol (120 mg), triethylamine (200 mg) and benzene (30 ml) was refluxed in a current of nitrogen for 7 h. The mixture was evaporated and the residue was chromatographed on silica gel. Elution with dichloromethane afforded (15b) (505 mg, 91 %) as prisms (from diethyl ether), m.p. 165 - 166°C (Found: C, 56.35; H, 4.61; N, 2.62. $C_{26}H_{26}F_3NO_7S$ requires C, 56.41; H, 4.73; N, 2.53 %), $\nu_{max.}$ ($CHCl_3$) 1770 (OAc), 1710 cm^{-1} (C=O); δ ($CDCl_3$) 2.06 (6H, s, 2 x Ac), 2.24 (3H, s, 9 - Me), 3.76 and 3.80 (each 1.5 H each s, OMe), and 7.00 - 7.50 (5H, m, 5 x ArH); m/e 553 (M^+).

1-Acetyl-1,3,5,6-tetrahydro-8-methoxy-9-methyl-7-nitro-6-phenylsulphoxymethyl-1-benzazocin-5(2H)one(8b). ——— A mixture of the sulphide (8a) (25 mg), m-chloroperbenzoic acid (10 mg) and dichloromethane (2 ml) was stirred at 0° under a nitrogen atmosphere for 15 h. The reaction mixture was evaporated and the residue was

chromatographed on silica gel. Elution with chloroform-methanol (98 : 2 v/v) afforded (8b) (22 mg, 85 %) as prisms (from ethanol), m.p. 176 - 179° (dec.), (Found: C, 57.11; H, 5.19; N, 5.75. $C_{22}H_{24}N_2O_6S \cdot H_2O$ requires C, 57.13; H, 5.66; N, 6.06 %); $\nu_{max.}$ ($CHCl_3$) 1720 (c=o), 1670 cm^{-1} (Ac); δ ($CDCl_3$) 2.08 (3H, s, Ac), 2.34 (3H, s, 9-Me), 3.82 (3H, s, OMe), 7.12 (1H, s, 10-H) and 7.20 - 8.20 (5H, m, 5 x ArH); m/e 318 (M^+ - C_6H_5SOH).

Reaction of 1-Acetyl-1,3,5,6-tetrahydro-8-methoxy-9-methyl-7-nitro-6-phenylsulphoxymethyl-1-benzazocin-5(2H) one (8b) with Acetic Anhydride. ——— A solution of the suphoxide (8b) (22 mg) in acetic anhydride (2 ml) was heated at 100°C under nitrogen for 30 min. The solution was evaporated under reduced pressure and the residue was chromotographed on silica gel to yield the enone (4c) (12 mg, 75 %), identical (m.p. and i.r., and n.m.r. spectra) to the sample described above.

5-Acetoxy-2,3-dihydro-8-hydroxy-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (10a) and 5,8-diacetoxy-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]-indole-9-carbaldehyde (10b). ——— A mixture of the quinone (9a) (259 mg), zinc dust (200 mg), sodium acetate (83 mg) in acetic anhydride (30 ml) was stirred at 100°C for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel. Elution with dichloromethane gave (10a) (110 mg, 36 %) as needles (from diethyl ether), m.p. 205 - 206°C (Found: C, 63.21; H, 5.58; N, 4.55. $C_{16}H_{17}NO_5$ requires C, 63,36; H, 5.65; N, 4.62 %), $\nu_{max.}$ ($CHCl_3$) 1760 (OAC), 1620 cm^{-1} (CHO); δ ($CDCl_3$) 2.10 and 2.34 (each 3H, each s, Ac and 6-Me), 4.86 (3H, s, OMe), 9.40 (1H, s, CHO) and 10.70 br (1H, s, OH); m/e 303 (M^+).

Further elution with chloroform gave (10b) (120 mg, 35 %) as needles (m.p. 173 - 174°C, from diethyl ether) (Found: C, 62.12; H, 5.58; N, 3.86. $C_{18}H_{19}NO_6$ requires C, 62.60; H, 5.55; N, 4.06 %), $\nu_{max.}$ ($CHCl_3$) 1760 (OAc) and 1655 cm^{-1} (CHO); δ ($CDCl_3$) 2.16, 2.36 and 2.48 (each 3H, each s, 2 x Ac and 6-Me), 3.84 (3H, s, OMe), and 9.98 (1H, s, CHO); m/e 345 (M^+). The phenolic compound (10a) was acetylated, to give the diacetate (10b), with acetic anhydride and pyridine in the usual manner.

5,8-Diacetoxy-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole (10c).—— (a) A mixture of the aldehyde (10b) (100 mg), boron trifluoride etherate (0.1 ml), and ethanedithiol (1 ml) was stirred at room temperature for 15 h. The mixture was poured in methanol (2 ml) and extracted with dichloromethane. The organic layer was washed with aqueous 10 % sodium hydroxide and aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with benzene as eluent

to afford (10c) (51 mg, 55 %) as needles, m.p. 123 - 124° (lit[3]. 123 - 124°), identical (i.r. and n.m.r. spectra) to that reported.

(b) A mixture of the aldehyde (10b) (35 mg), tris(triphenylphosphine)chlororhodium (100 mg) and toluene (10 ml) was refluxed under nitrogen for 20 h. The solvent was evaporated and the residue was chromatographed on silica gel with benzene as eluent to give (10c) (26 mg, 81 %) identical (i.r. and n.m.r. spectra and t.l.c.) to the sample described above.

1,2,3,4,5,6-Hexahydro-5,5,8-trimethoxy-9-methyl-6-methylene-1-benzazocin-7,10-dione (17b). ——— A mixture of the acetate (14) (50 mg), lithium aluminium hydride (10 mg) and tetrahydrofuran (2 ml) was stirred at room temperature for 3 h under nitrogen. Excess lithium aluminium hydride was decomposed with aqueous tetrahydrofuran and the reaction mixture was extracted with dichloromethane. The extract was washed with aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was chlormatographed on alumina (neutral, grade III) to yield (17b) (11 mg, 35 %) as violet needles, m.p. 148 - 149°C (from diethyl ether) (Found: C, 62.67; H, 6.77; N, 4.56. $C_{16}H_{21}NO_5$ requires C, 62.52; H, 6.88; N, 4.56 %), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), and 1640 and 1575 cm^{-1} (c=o); δ (CCl_4) 1.82 (3H, s, 9-Me), 3.10 and 3.22 (each 3H, each s, 2 x 5 -OMe), 4.14 (3H, s, 8-OMe), and 5.14 and 5.90 (each 1H, each d, J 2Hz, 2 x olefinic H); m/e 307 (M^+).

1,2,3,4,5,6-Hexahydro-5-hydroxy-9-methyl-6-methylene-1-benzazocin-7,10-dione (16). ——— A mixture of the enone (13) (45 mg), lithium aluminium hydride (10 mg), and tetrahydrofuran (5 ml) was stirred at room temperature for 2h under nitrogen. Work up as above afforded the quinone (16) (16 mg, 60 %) as violet needles, m.p. 155 - 156°C (Found: C, 63.72; H, 6.74; N, 5.41. $C_{16}H_{17}NO_4$ requires C, 63.86; H, 6.51; N, 5.31 %), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), and 1655, 1740 and 1570 cm^{-1} (c=o); δ ($CDCl_3$) 1.86 (3H, s, 9-Me), 4.10 (3H, s, OMe), 5.14 and 5.70 (each 1H, each d, J 2Hz, 2 x olefinic H), and 6.30 br (1H, s, NH); m/e 263 (M^+).

Transannular Cyclisation of 1,2,3,4,5,6-hexahydro-5-hydroxy-9-methyl-6-methylene-1-benzazocin-7,10-dione (16). ——— A mixture of the quinone (16) (10 mg), aqueous 10 % hydrochloric acid (1 ml), and acetone (1 ml) was stirred at room temperature for 24 h. The mixture was extracted with dichloromethane, washed with water, dried (Na_2SO_4), and evaporated to give a solid. Recrystallisation from diethyl ether afforded (9b) (3 mg, 32 %) as red needles, identical (m.p., t.l.c., and spectral data) to the sample reported.[3]

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8. Tetrafluoroboric acid or acetic acid did not effect this reaction. (cf. F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, J. Amer. Chem. Soc., 1977, 99, 4835.)

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