A CONVENIENT PHOTOSYNTHESIS OF AZIRIDINO-PYRROLO[1,2-a]BENZ[f]-INDOLOQUINONES AS MODEL MITOMYCINS IN A ONE-POT REACTION

Mitsuo Akiba* and Toyozo Takada

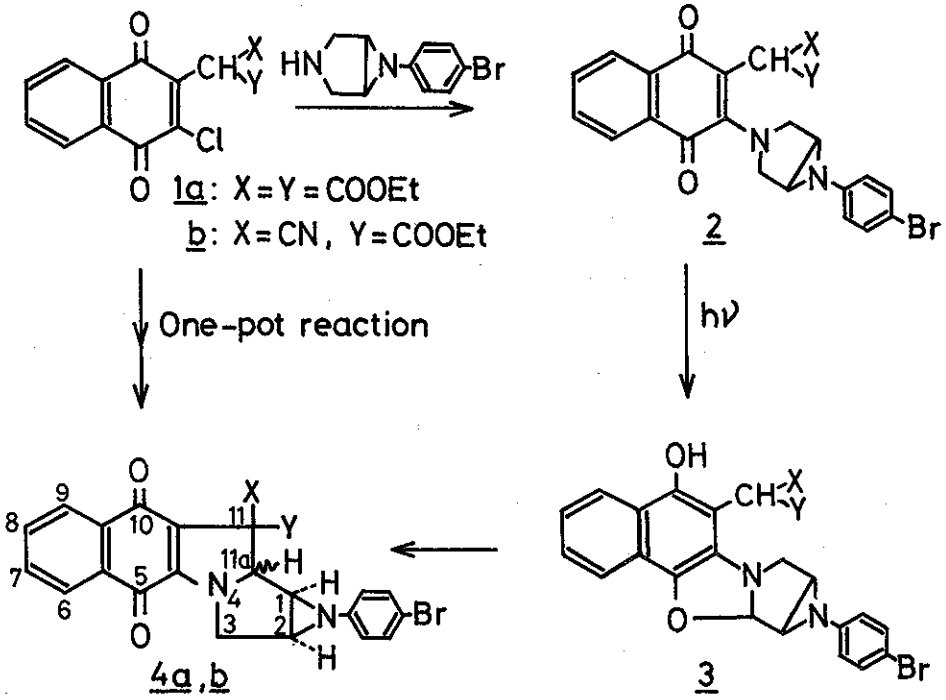
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo, 192-03, Japan

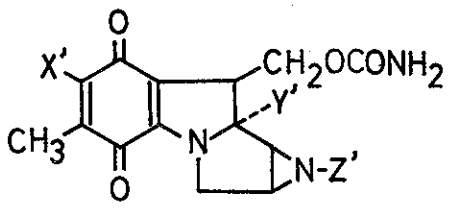
The aziridino-pyrrolo[1,2-a]benz[f]indoloquinones (4b) were photosynthesized as model mitomycins from 2-chloro-3-ethoxycarbonylcyanomethyl-1,4-naphthoquinone (1b) and 6-(4-bromophenyl)-3,6-diazabicyclo[3.1.0]-hexane in a one-pot reaction.

In the synthetic studies on mitomycin antibiotics (5), up to the present, a number of indoloquinones[1] have been prepared as mitomycin analogues. However, most of the published routes were concerned with the formation of the tricyclic pyrrolo[1,2-a]indole and indoloquinone system and their yields did not seem to be satisfactorily high. Furthermore, the various efforts to build up the tetracyclic quinones by adding an aziridino moiety to the tricyclics were not fruitful.

More recently, we have shown that the photolysis[2] of certain amino-substituted 1,4-naphthoquinones afforded the naphthoxazolines which was converted to the heterocyclic quinones in the protic and polar solvents. In case of the photolysis of the aminoquinone (2a) prepared from (1a), the aziridino-pyrrolo[1,2-a]benz[f]indoloquinone (4a)[3] having the complete ring system of mitomycins was obtained in good yields. These consecutive reactions(amino substitution, photolysis, and ring conversion) may be also carried out continuously as a one-pot reaction.

We now wish to report an example of this novel type of the photosynthesis of aziridino-pyrrolo[1,2-a]benz[f]indoloquinones as model mitomycins in a one-pot reaction. Schematically the overall process can be represented as follow:





5

The reaction solution of 2-chloro-3-ethoxycarbonylcyanomethyl-1,4-naphthoquinone (1b)[4] and 2 equimolar amount of 6-(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hexane[5] in ethanol-chloroform, without the isolation of the amino-substituted 1,4-naphthoquinone (2b), was irradiated with a high pressure mercury lamp through Pyrex glass in a stream of nitrogen for 2 hr. After the irradiated solution of (2b) had been allowed to stand more than 2 weeks at room temperature, four isomers due to the different substituents at C-11 position of the aziridino-pyrrolo[1,2-a]benz[f]indoloquinone (4b) were isolated by preparative thin layer chromatography. The each structural assignment for the isomers of (4b) was based on their analytical and spectral data which were in good agreement with their formulation. (4b-1): 8.7% yield, mp 240-242° (from EtOH-CH_3COCH_3); ir 1740 (ester), 1679, and 1632 (CO) cm^{-1}; nmr ($CDCl_3$) 1.40 (3H, t, $COOCH_2\underline{CH_3}$), 3.46 (2H, broad s, C_1-H and C_2-H), 3.88 (1H, s, C_3-H), 3.95 (1H, d, J_{C_2,C_3} = 2.5 Hz, C_3-H'), 4.42 (2H, q, $COO\underline{CH_2}CH_3$), 4.74 (1H, C_{11a}-H), 6.88-7.36 (4H, J_{AB}= 8.0 Hz, Ar-H), and 7.68-8.04 (4H, m, Ar-H) ppm; ms m/e 503 (M^+). (4b-2): 21.8% yield, mp 237-239° (from EtOH-CH_3COCH_3); ir 1738 (ester), 1680, and 1632 (CO) cm^{-1}; nmr ($CDCl_3$) 1.32 (3H, t, $COOCH_2\underline{CH_3}$), 2.96 (1H, d, $J_{1,2}$= 4.5 Hz, C_1-H), 3.32 (1H, d,d, $J_{1,2}$= 4.5 Hz, $J_{2,3}$= 2.5 Hz, C_2-H), 3.82 (1H, d, $J_{2,3}$= 2.5 Hz, C_3-H'), 3.86 (1H, s, C_3-H), 4.30 (2H, q, $COO\underline{CH_2}CH_3$), 4.88 (1H, s, C_{11a}-H), 6.85-7.34 (4H, J_{AB}= 8.0 Hz, Ar-H), and 7.68-8.08 (4H, m, Ar-H) ppm; ms m/e 503 (M^+). (4b-3): 9.6% yield, mp 266-268° (from EtOH-CH_3COCH_3); ir 1760 (ester), 1678, and 1630 (CO) cm^{-1}; nmr ($CDCl_3$) 1.46 (3H, t, $COOCH_2\underline{CH_3}$), 3.12 (1H, d,d, $J_{2,3}$ = 2.5 Hz, $J_{1,2}$= 4.5 Hz, C_2-H), 3.32 (1H, d,d, $J_{11a,1}$= 2.5 Hz, $J_{1,2}$= 4.5 Hz, C_1-H), 3.58 (1H, d,d, $J_{2,3}$= 2.5 Hz, $J_{3,3}$= 14.0 Hz, C_3-H'), 4.46 (2H, q, $COO\underline{CH_2}CH_3$), 4.65 (1H, d, J = 14.0 Hz, C_3-H), 4.68 (1H, d, $J_{11a,1}$= 2.5 Hz, C_{11a}-H), 7.10-7.33 (4H, J_{AB}= 8.0 Hz, Ar-H), and 7.70-8.80 (4H, m, Ar-H) ppm; ms m/e 503 (M^+). (4b-4): trace mp 260-261° (from EtOH-CH_3COCH_3); ir 1760 (ester), 1677, and 1630 (CO) cm^{-1}; nmr ($CDCl_3$) 1.16 (3H, t, $COOCH_2\underline{CH_3}$), 2.94 (1H, d,d, $J_{2,3}$= 2.5 Hz, $J_{1,2}$= 4.5 Hz, C_2-H),

3.22 (1H, d,d, $J_{11a,1}$= 2.5 Hz, C_1-H), 3.58 (1H, d,d, $J_{2,3}$= 2.5 Hz, $J_{3,3}$= 14.0 Hz, C_3-H'), 4.24 (2H, q, $COOCH_2CH_3$), 4.50 (1H, d, $J_{3,3}$= 14.0 Hz, C_3-H), 4.96 (1H, d, $J_{11a,1}$= 2.5 Hz, C_{11a}-H), 6.78-7.28 (4H, J_{AB}= 8.0 Hz, Ar-H), and 7.64-8.00 (4H, m, Ar-H) ppm; ms m/e 503 (M^+).

The configuration of the different substituents at C-11 position in each isomer of (4b) was not established. However, the stereochemistry of C_{11a}-H and C_1-H was assigned by comparing the nmr spectra of (4b) and the natural product. The more polar isomers on silica gel having the characteristic coupling constants[1,6] (2.5 Hz at 4.68 ppm in (4b-3) and 4.96 ppm in (4b-4)) were assigned as cis-pyrrolidine, whereas the less polar isomers, (4b-1) and (4b-2), as trans-pyrrolidine because of the absence of them. The similar photolysis in ethanol gave only cis-isomers, (4b-3) and (4b-4), in good yields. It is noteworthy that the formation of the trans- and cis-isomer was effected by the solvents.

Further study on the total synthesis of mitomycin and the implication of the one-pot reaction are being carried out.

Acknowledgement Our sincere thanks are offered to Prof. S. Ohki for his continuous interest and encouragement on this work.

References

1 See reference 3, references contained therein.

2 M. Akiba, Y. Kosugi, M. Okuyama, and T. Takada, Heterocycles, 1977, 6, 1113.

3 M. Akiba, Y. Kosugi, M. Okuyama, and T. Takada, J. Org. Chem., submitted.

4 G.A. Reynolds, J.A. Allan, and R.E. Adel, J. Org. Chem., 1965, 30, 3819.

5 P. Scheiner, Tetrahedron, 1968, 24, 2757.

6 J.W. Lown and A. Begleiter, Can. J. Chem., 1974, 52, 2331.

Received, 8th August, 1977