A Convenient Synthesis of 7-Methoxymitosene by the Photolysis of Aminobenzoquinones

Mitsuo Akiba,* Satoshi Ikuta, and Toyozo Takada

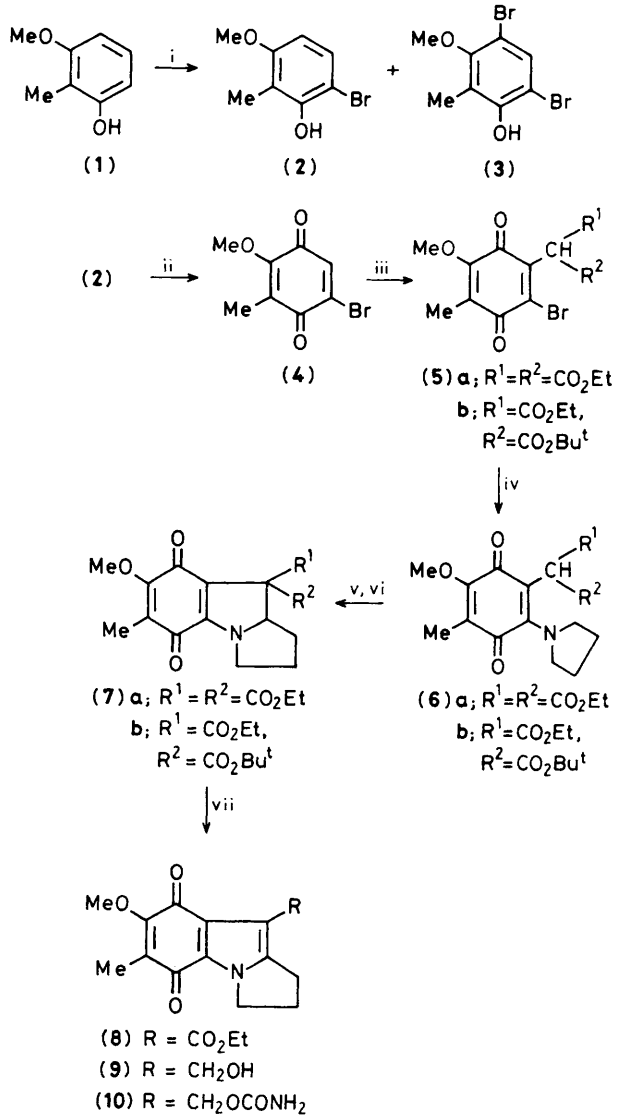
Tokyo College of Pharmacy, 1432–1, Horinouchi Hachioji, Tokyo, 192–03, Japan

A simple method for the preparation of pyrrolo[1,2-*a*]indoloquinone derivatives using the photolysis of amino-quinones has led to a formal synthesis of 7-methoxymitosene.

In synthetic studies on mitomycin antibiotics,[1] which contain several unique structural features, we have shown that the photolysis of amino-1,4-naphtho- and -benzo-quinones having the active methylene group at the 2-position provides a preparative route to heterocyclic quinones.[2] In this communication we describe the application of this photo-induced reaction to freshly prepared pyrrolidinylbenzoquinones (**6**) as a simple synthesis of 7-methoxymitosene (**10**).

Our initial approach to (**10**) focused on the preparation of (**7**) as outlined in Scheme 1. Treatment of the phenol (**1**)[3] with bromine–t-butylamine[4] at −78 °C afforded the bromophenol (**2**) (60%, m.p. 47 °C) in addition to the dibromophenol (**3**) (20%, m.p. 74 °C). Compound (**2**) was oxidized with potassium nitrosyldisulphonate–KH_2PO_4($\frac{1}{6}$ M)–acetone–H_2O to give the quinone (**4**)† (73%, m.p. 65 °C). Treatment of (**4**) with

† Satisfactory spectral and analytical data were obtained.



Scheme 1. *Reagents:* i, Br_2, Bu^tNH_2, −78 °C; ii, $(SO_3K)_2NO$, 1/6 M KH_2PO_4, Me_2CO–H_2O; iii, $TlCH(R^1)(R^2)$ ($R^1 = R^2 = CO_2Et$ or $R^1 = CO_2Et$, $R^2 = CO_2Bu^t$), THF; iv, pyrrolidine, $CHCl_3$; v, *hν*, EtOH; vi, SiO_2, EtOH; vii, CF_3CO_2H, CH_2Cl_2.

thallium diethylmalonate in tetrahydrofuran (THF) gave (**5a**)† (40%, a yellow oil), which reacted with pyrrolidine to yield the amino-quinone (**6a**)† (85%, a purple oil). A solution of (**6a**) in ethanol was irradiated with a high pressure mercury lamp through Pyrex glass. This irradiated solution was retained on a silica gel column for a few days, and then eluted with ethyl acetate to afford (**7a**)‡ (68%, m.p. 171 °C). De-esterification of (**7a**) with sodium cyanide or magnesium chloride in dimethyl sulphoxide[5] followed by oxidation failed to give the required product (**8**). Therefore, the pyrrolidinyl-benzoquinone (**6b**)† was prepared from (**4**) and the thallium salt of ethyl t-butylmalonate by the same method in a moderate yield. Photolysis of (**6b**) afforded the diastereoisomers of the pyrroloindoloquinone, (**7b**)-(I)‡ (40%, m.p. 103 °C) and (**7b**)-(II)‡ (32%, m.p. 156 °C), in the ratio 5 : 4 after chromatography on silica gel. Structural assignments have not yet been made. On treatment with trifluoroacetic acid, however, each stereoisomer was converted into the same product (**8**)‡ (m.p. 164 °C), which was identical with an authentic sample (lit.[6] m.p. 165—166 °C). Recently, the transformation of (**8**) to (**9**) and 7-methoxymitosene (**10**) was reported by Coates and MacManus.[6] Consequently, this sequence constitutes a formal synthesis of 7-methoxymitosene.

Received, 7th March 1983; Com. 295

References

1 R. W. Franck, *Prog. Chem. Org. Nat. Prod.*, 1979, **38**, 1; K. Takahashi and T. Kametani, *Heterocycles*, 1979, **13**, 411; J. R. Lury and H. Rapoport, *J. Org. Chem.*, 1982, **47**, 2404. Recent references are contained herein.
2 M. Akiba, Y. Kosugi, M. Okuyama, and T. Takada, *J. Org. Chem.*, 1978, **43**, 181; M. Akiba, S. Ikuta, and T. Takada, *Heterocycles*, 1981, **16**, 1579.
3 A. Rashid, *J. Chem. Soc.*, 1967, 1323.
4 D. E. Pearson, *J. Org. Chem.*, 1967, **32**, 2358.
5 W. S. Johnson, C. A. Harbert, and R. D. Stpanovic, *J. Am. Chem. Soc.*, 1968, **90**, 5279.
6 R. M. Coates and P. A. MacManus, *J. Org. Chem.*, 1982, **47**, 4822.

‡ Compound (**7a**): i.r. ν_{max}(KBr) 1720, 1650 (C=O) cm^{-1}; *m/z* 377 M^+; ^1H n.m.r. δ($CDCl_3$) 1.30 (6H, t, *J* 7.5 Hz, Me × 2), 1.87 (3H, s, Me), 1.70—2.20 (4H, m, CH_2 × 2), 3.63 (2H, m, CH_2N), 4.12 (3H, s, OMe), 4.26 (4H, q, *J* 7.5 Hz, OCH_2 × 2), 4.80 (1H, m, CHN). Compound (**7b**)-(I): i.r. ν_{max} (KBr) 1742, 1723, 1660, 1640, 1580 cm^{-1}; *m/z* 405 M^+; ^1H n.m.r. δ($CDCl_3$) 1.28 (3H, t, *J* 7.5 Hz, Me), 1.46 (9H, s, Bu^t), 1.84 (3H, s, Me), 1.84—2.20 (4H, m, CH_2 × 2), 3.60 (2H, m, NCH_2), 4.08 (3H, s, OMe), 4.26 (2H, q, *J* 7.5 Hz, CH_2), 4.80 (1H, m, CH). Compound (**7b**)-(II): i.r. ν_{max} (KBr) 1747, 1708, 1650, 1623, 1560 cm^{-1}; *m/z* 405 M^+. The n.m.r. spectrum is very similar to that of (**7b**)-(I). Compound (**8**): i.r. ν_{max} (KBr) 1718, 1662, 1640, 1610 cm^{-1}; *m/z* 303 M^+; ^1H n.m.r. δ($CDCl_3$) 1.36 (3H, t, *J* 7.5 Hz, Me), 1.96 (3H, s, Me), 2.56 (2H, quintet, *J* 7.5 Hz, $NCH_2CH_2CH_2$), 3.10 (2H, t, *J* 7.5 Hz, CH_2), 4·06 (3H, s, OMe), 4.28 (2H, t, *J* 7.5 Hz, NCH_2), 4.32 (2H, q, *J* 7.5 Hz, CO_2CH_2Me).