

Synthetic Approaches to Aclacinomycin and Pyrromycin Antitumour Antibiotics *via* Diels–Alder Reactions of 6-Alkoxy-2-pyrones: Total Synthesis of Chrysophanol, Helminthosporin and Pachybasin

By MICHAEL E. JUNG* and JOHN A. LOWE

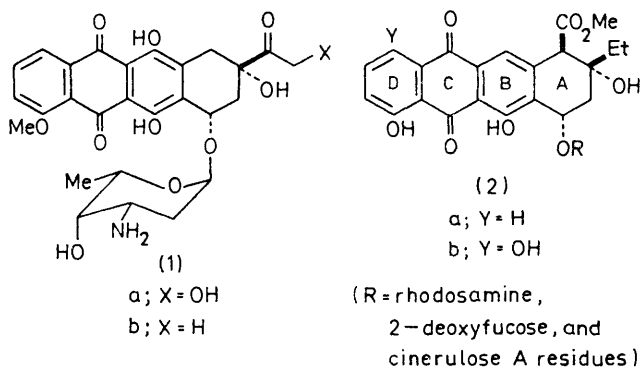
(Department of Chemistry, University of California, Los Angeles, California 90024)

Summary The Diels–Alder reaction of a 6-alkoxy-2-pyrone (**6**) with quinones (**3a–c**) has been investigated as a synthetic approach to the aclacinomycin and pyrromycin antibiotics (**2a** and **b**) and has resulted in efficient total syntheses of chrysophanol (**7a**), helminthosporin (**7b**), and pachybasin (**7c**).

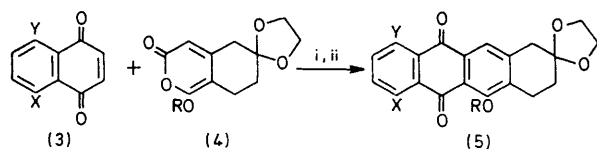
CURRENTLY considerable effort is being focused on synthetic approaches to adriamycin (**1a**) and daunomycin (**1b**), two members of the rhodomycinone subgroup of the anthracycline antibiotics which are very effective in cancer chemo-

therapy.¹ However, many other anthracycline antibiotics exhibiting interesting biological activity do not belong to the rhodomycinone subgroup but rather to the aklavinone (**2a**), and pyrromycinone (**2b**) subgroups. For example, aclacinomycin A (**2a**),² and cinerubin A (**2b**)³ exhibit significant tumour-inhibitory properties, the former being perhaps more effective than adriamycin in treating cancer because of its low cardiotoxicity.² Almost all the present synthetic approaches to the rhodomycinone family⁴ are not applicable to the aklavinone or pyrromycinone families, which lack a hydroxy-group in ring B at C-11. We report now a new synthetic approach to molecules such as (**2**), which involves, as the key step, a Diels–Alder reaction between 6-alkoxy-2-pyrones and naphthoquinones. This approach has resulted in efficient total syntheses of chrysophanol (**7a**), helminthosporin (**7b**), and pachybasin (**7c**).

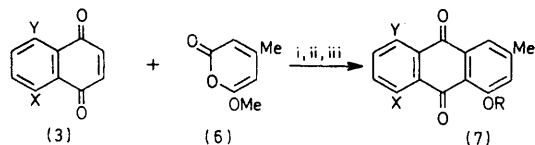
Since the Friedel–Crafts approach to these molecules is unsatisfactory,⁵ we have developed the alternative convergent synthesis in Scheme 1, top. Juglone (**3a**)⁶ and naphthazarin (**3b**),⁷ both readily available, serve as precursors to the c,d portion, while a suitably substituted pyrone (**4**) serves as the a,b precursor. Diels–Alder addition between these halves should lead to a much higher yield of the tetracyclic system than a Friedel–Crafts process, not only because both bonds are formed in one step, but also because of the milder conditions. Studies with the model systems herein



described provide information on the three critical features of this general approach: the preparation of pyrones such as (4), their Diels–Alder reaction with quinones, and the regioselectivity, if any, of these reactions.



a; X = OH, Y = H
b; X = Y = OH



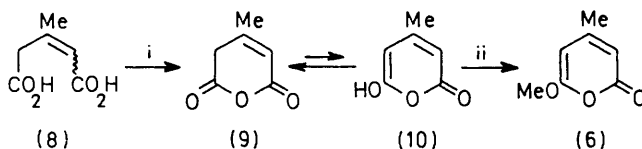
a; X = OH, Y = H
b; X = Y = OH
c; X = Y = H
d; X = H, Y = OAc

a; X = OH, Y = H, R = H (62%)
b; X = Y = OH, R = H (38%)
c; X = Y = H, R = H (64%)
d; X = H, Y = OH, R = Me } (13.5%)
e; X = OH, Y = H, R = Me }

SCHEME 1. Reagents: i, heat ($-CO_2$); ii, $Ag_2O-MgSO_4$; iii (for **3a–c**), 48% HBr–HOAc; iii (for **3d**), 2M NaOH.

Whereas 3-methoxy-⁸ and 3-hydroxy-pyrone⁹ are known to undergo Diels–Alder reactions with quinones, their synthesis precludes the preparation of the dialkyl-substituted derivatives necessary for the construction of (2).¹⁰ Since 6-hydroxy-2-pyrone is formally a tautomer of the anhydride of glutamic acid, many derivatives of which can be easily prepared,¹¹ this system presented potentially a much more general alternative. β -Methylglutaconic anhydride (9) [prepared from the acid (8)¹² by heating with acetyl chloride¹³] did not undergo Diels–Alder reactions with quinones *via* its tautomeric form (10). However, the molecule could be trapped in the hydroxy-pyrone form (Scheme 2) by reaction of the tautomeric mixture of (9) and (10) with ethereal diazomethane to produce 6-methoxy-4-methylpyran-2-one

(6) in 67.5% yield [m.p. 54–55 °C; δ ($CDCl_3$) 2.16 (3H, br s), 3.87 (3H, s), 5.30 (1H, m), and 5.71 (1H, m); ν_{max} (liq. film) 1740, 1640, and 1540 cm^{-1} ; satisfactory elemental analyses were obtained].



SCHEME 2. Reagents: i, MeCOCl, heat; ii, $CH_2N_2-Et_2O$.

The pyrone (6) reacted readily with quinones to form several natural products (Scheme I, bottom). Diels–Alder addition to naphthoquinone (3c) followed by oxidation ($Ag_2O-MgSO_4$) and demethylation (48% HBr–HOAc) furnished pachybasin (7c)¹⁴ in 64% overall yield. The regiochemical outcome of this cycloaddition was determined by the Diels–Alder reaction of (6) with juglone (3a) which, after oxidation and demethylation, gave a 62% overall yield of chrysophanol (7a), identified as its diacetate by m.p.¹⁵ and n.m.r. spectroscopy.¹⁶ Although regioselectivity is well known in Diels–Alder reactions of juglone,¹⁷ the absence of the undesired isomer was significant since regiospecificity of this type is important for the synthesis of aklavinone. However, reaction of (6) with juglone acetate (3d) followed by oxidation and acetate hydrolysis (2M NaOH) furnished a *ca.* 1 : 1 mixture of the two possible adducts, ziganein methyl ether (7d)¹⁸ and chrysophanol methyl ether (7e) in low yield (13.5%). Finally, as a model for the pyrromycinone structure, Diels–Alder reaction with naphthazarin (3b) and subsequent oxidation and demethylation afforded a 38% overall yield of helminthosporin, (7b).¹⁹

Thus we have shown that the pyrone approach to the anthracycline skeleton is a synthetic possibility.

J. A. L. thanks the U.C.L.A. Committee on Research for a Chancellor's Patent Fund Grant.

(Received, 5th September 1977; Com. 926.)

¹ D. W. Henry, 'Adriamycin,' in 'Cancer Chemotherapy,' ed. A. C. Sartorelli, American Chemical Society, Washington, D.C., 1976.

² T. Oki, Y. Matsuzawa, A. Yoshimoto, K. Numata, I. Kitamura, S. Hori, A. Takamatsu, H. Umezawa, M. Ishizuka, H. Naganawa, H. Suda, M. Hamada, and T. Takeuchi, *J. Antibiotics*, 1975, **28**, 830.

³ F. Strelitz, H. Flon, U. Weiss, and I. N. Asheshov, *J. Bacteriol.*, 1956, **72**, 90.

⁴ C. M. Wong, R. Schwenk, D. Popien, and T.-L. Ho, *Canad. J. Chem.*, 1973, **51**, 466; C. M. Wong, D. Popien, R. Schwenk, and J. Te Raa, *ibid.*, 1971, **49**, 2712; A. S. Kende, J. Belletire, T. J. Bentley, E. Hume, and J. Airey, *J. Amer. Chem. Soc.*, 1975, **97**, 4425; A. S. Kende, Y.-G. Tsay, and J. E. Mills, *ibid.*, 1976, **98**, 1967; T. H. Smith, A. N. Fujiwara, D. W. Henry, and W. W. Lee, *ibid.*, p. 1969; T. R. Kelly, J. W. Gillard, R. N. Goerner, and J. M. Lyding, *ibid.*, 1977, **99**, 5513; W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, *J. Org. Chem.*, 1976, **41**, 2296; M. E. Jung and J. A. Lowe, *ibid.*, 1977, **42**, 2371; R. D. Gleim, S. Trenbeath, R. S. D. Mittal, and C. J. Sih, *Tetrahedron Letters*, 1976, 3385; T. R. Kelly, R. N. Goerner, J. W. Gillard, and B. K. Prazak, *ibid.*, p. 3869; T. R. Kelly, J. W. Gillard, and R. N. Goerner, *ibid.*, p. 3873; A. S. Kende and Y.-G. Tsay, *J.C.S. Chem. Comm.*, 1977, 140.

⁵ Z. Horii, H. Hokusui, and T. Momose, *Chem. Pharm. Bull. (Japan)*, 1968, **16**, 1262; Z. Horii, T. Momose, and Y. Tamura, *ibid.*, 1965, **13**, 797.

⁶ H.-J. Teuber and N. Götz, *Chem. Ber.*, 1954, **87**, 1236.

⁷ L. F. Fieser and J. T. Dunn, *J. Amer. Chem. Soc.*, 1937, **59**, 1016.

⁸ P. Bosshard, S. Fumagalli, R. Good, W. Treub, W. v. Philipsborn, and C. H. Eugster, *Helv. Chim. Acta.*, 1964, **47**, 769.

⁹ E. J. Corey and A. P. Kozikowski, *Tetrahedron Letters*, 1975, 2389.

¹⁰ R. H. Wiley and C. H. Jarboe, *J. Amer. Chem. Soc.*, 1965, **78**, 2398.

¹¹ L. F. Cavalieri, *Chem. Rev.*, 1947, **41**, 525.

¹² R. H. Wiley and N. R. Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 3531; F. Feist, *Annalen*, 1906, **345**, 60.

¹³ N. Bland and J. F. Thorpe, *J. Chem. Soc.*, 1912, **101**, 856.

¹⁴ S. Shibata and M. Takido, *Pharm. Bull. (Japan)*, 1955, **3**, 156.

¹⁵ J. Breen, J. C. Dacre, H. Raistrick, and G. Smith, *Biochem. J.*, 1955, **60**, 618.

¹⁶ Y. Ogihara, N. Kobayashi, and S. Shibata, *Tetrahedron Letters*, 1968, 1881.

¹⁷ H. H. Inhoffen, H. Muxfeldt, H. Schaefer, and H. Kramer, *Croat. Chem. Acta.*, 1957, **29**, 329; H. Muxfeldt, *Angew. Chem.*, 1962, **74**, 825.

¹⁸ S. Imre, A. Öztunc, and N. Büyüktimkin, *Phytochem.*, 1973, **13**, 681.

¹⁹ K. Chandrasenan, S. Neelakantan, and T. R. Seshadri, *J. Indian Chem. Soc.*, 1961, **38**, 907.