*Aust. J. Chem.*, 1984, **37**, 1699–707

# The Regiospecific Synthesis of an Anthraquinone Based upon the Elaboration of the Adduct of 1-Acetoxyisobenzofuran with *p*-Benzoquinone Monoacetal*

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*Abstract*

1-Acetoxyisobenzofuran (4) reacts regiospecifically with 4,4-dimethoxycyclohexa-2,5-dienone (*p*-benzoquinone monoacetal) (6) to yield a single $[4\pi+2\pi]$ cycloadduct with *endo* stereochemistry. Treatment of this adduct (7) with sodium methoxide formed 1,10-dihydroxy-4,4-dimethoxy-4a,10-dihydroanthracen-9(4*H*)-one (12), which was oxidized by the Corey–Fleet reagent to afford 1-hydroxy-4-methoxyanthracene-9,10-dione. This model reaction illustrates the potential of this approach to the regiospecific synthesis of anthraquinones. Attempts to introduce methoxy substituents into the anthraquinone by using 4- and 7-methoxy-1-acetoxyisobenzofuran, isobenzofurans described for the first time, were less successful. This limitation is discussed.

## Introduction

One objective in our approach to the synthesis of anthracycline antibiotics has been to develop routes in which the two carbon–oxygen bonds of the C-ring quinone moiety are introduced in the one step. This has distinct advantages, especially where the quinone function can be formed directly. Even in cases where the oxygen atoms are introduced at a lower level of oxidation and it is necessary to effect secondary oxidations to form the quinone, this can be sufficiently mild so as to remain compatible with other molecular features found in anthracyclines. One approach we have employed has used the $[4\pi+2\pi]$ cycloaddition products formed from 1-substituted isobenzofurans and quinones. However, a severe limitation was uncovered when this approach was applied to 1-acetoxyisobenzofuran, and this has been reported elsewhere.[1] We have subsequently established and reported that 1-substituted isobenzofurans react regiospecifically with quinone monoacetals to yield stable 1 : 1 adducts.[2] This finding substantially increases the potential of the method since cycloaddition occurs with complete regioselectivity. In previous applications of isobenzofurans to the synthesis of anthracycline antibiotics, e.g., (1), the isobenzofurans have been used as a naphthalene synthon in the AB + CD condensation[3] (Scheme 1). As a result, the C-ring is made fully aromatic but devoid of oxygen substituents; the quinone functionality is subsequently introduced by a separate, and vigorous,

* Part VII of Isobenzofurans (Part VI, *J. Chem. Soc., Chem. Commun.*, 1982, 1195).

[1] Russell, R. A., Marsden, D. E., Sterns, M., and Warrener, R. N., *Aust. J. Chem.*, 1981, **34**, 1223.
[2] Warrener, R. N., Hammer, B. C., and Russell, R. A., *J. Chem. Soc., Chem. Commun.*, 1981, 942.
[3] Kende, A. S., Curran, D. P., Tsay, Y. G., and Mills, J. E., *Tetrahedron Lett.*, 1977, 3537.

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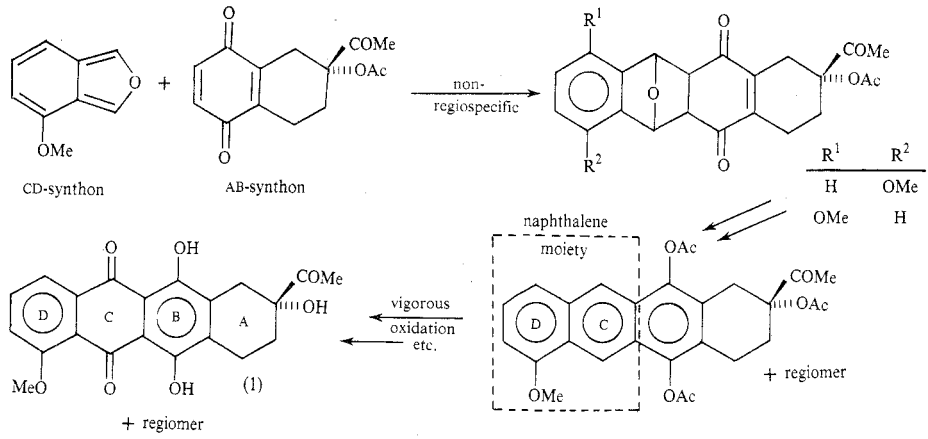
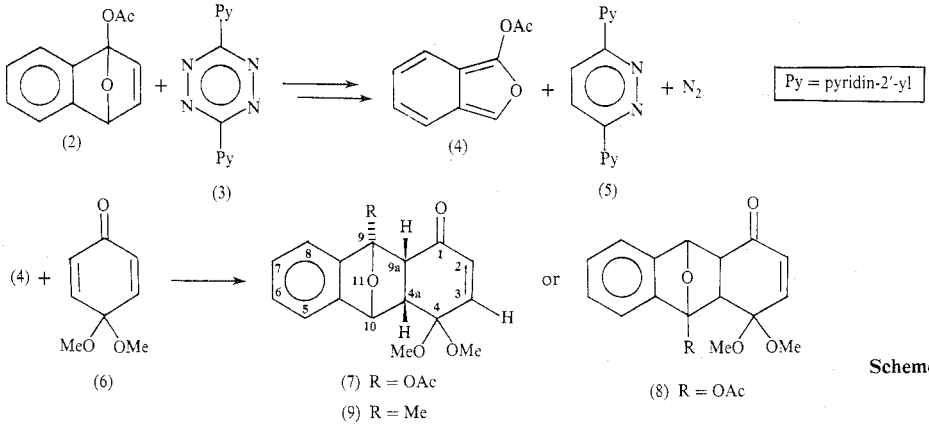
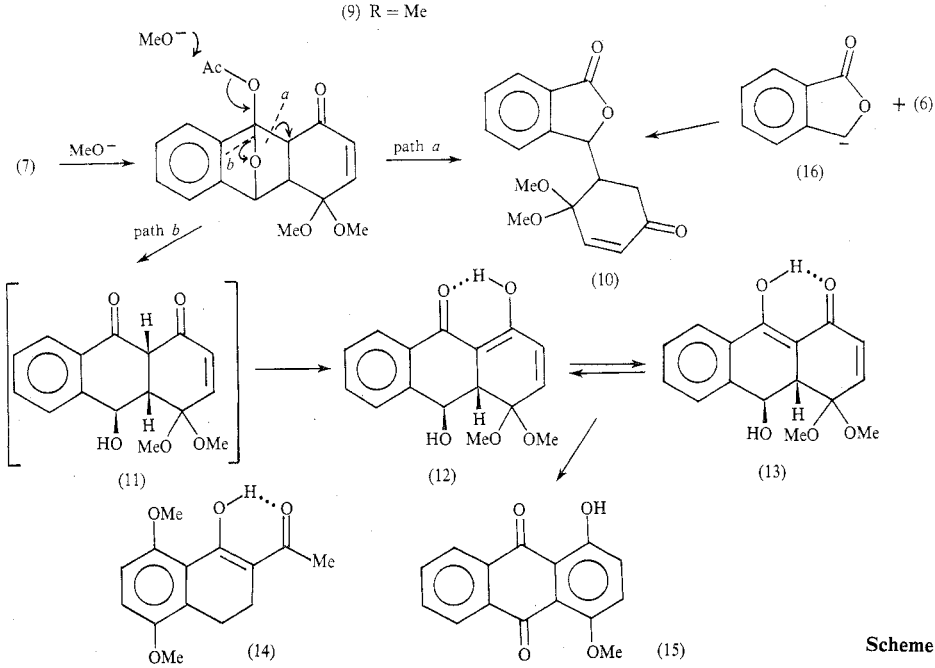



**Scheme 1.** Non-regiospecific route to 7-deoxydaunomycinone (1).[3]




**Scheme 2**




**Scheme 3**

oxidation step. The second drawback to this latter approach is that the cycloaddition step lacks regiospecificity.

In the present paper, we report our results on the preparation of the adduct of 1-acetoxyisobenzofuran with *p*-benzoquinone monoacetal, and its use as a model for the production of regiospecifically substituted anthraquinones.

## Results and Discussion

The reaction of 1-acetoxy-1,4-dihydro-1,4-epoxynaphthalene (2) with 3,6-di(pyridin-2′-yl)-*s*-tetrazine (3) in the presence of 4,4-dimethoxycyclohexa-2,5-dienone (6) yielded a single crystalline adduct with a molecular composition consistent with either structure (7) or (8) (Scheme 2).

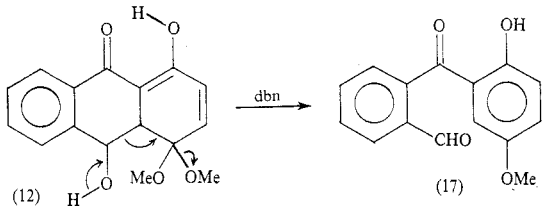
The stereochemistry of this adduct was established by examination of the $^1$H n.m.r. spectrum which contained resonances ($\delta$ 5·10, 3·48) corresponding to the vicinal protons H 10 and H 4a respectively. The existence of a $^3J$ coupling (4·6 Hz) between these two protons is consistent only with the *endo* stereochemistry.[4] This assignment is further supported by the chemical shifts of the resonances for the vinylic protons H 2 and H 3 ($\delta$ 5·03, 5·38) which reflect the shielding effect of the proximate benzene ring, a feature found only in *endo* adducts of this type.[5] The regiospecificity of this cycloaddition rested upon evaluation of the structures (7) and (8) and was more difficult to establish. It relied upon high-field $^1$H n.m.r. assignments to the unknown and a comparison with the related model adduct (9) of known structure[2] in which a key long-range $^4J$ coupling (1·5 Hz) between H 3 and H 4a is observed. In the present case, the proton resonance at $\delta$ 3·48 was assigned to H 4a by virtue of its two vicinal couplings ($^3J_{4a,9a}$ 9·5, $^3J_{4a,10}$ 4·6 Hz). The presence of the additional long-range interaction with H 3 ($^4J$ 1·5 Hz) was established by single-frequency decoupling and enabled the adduct to be unequivocally assigned structure (7).

The adduct (7) reacted cleanly with sodium methoxide in methanol to yield a major product and traces of the phthalide (10) [identical with material formed from phthalide (16) and 4,4-dimethoxycyclohexa-2,5-dienone, see Experimental]. The minor product (10) is assumed to arise from deacetylation and subsequent cleavage of the C 9–C 9a bond (Scheme 3, path *a*). The major product is formed from the alternative C 9–O 11 cleavage (Scheme 3, path *b*). The $^1$H n.m.r. spectrum of the major product contained two hydroxy group proton resonances, one of which ($\delta$ 16·4) was indicative of a strongly hydrogen-bonded enolic proton.[4] Furthermore, two three-proton singlet resonances ($\delta$ 2·78, 2·94) indicated that the dimethyl acetal group remained intact. The resonance at $\delta$ 5·57 was assigned to a proton of a benzylic methine group to which a hydroxy group was attached, and its coupling constant ($^3J$ 12·6 Hz) attributed to the quasi-axial–equatorial coupling with a vicinal proton neighbour. Both $^1$H and $^{13}$C n.m.r. spectra confirmed the presence of two vinylic CH groups, and structure (12) or (13) can accommodate these findings, each being formed by tautomerism of the diketone (11) (Scheme 3, path *b*). $^{13}$C n.m.r. data support either structure: in particular doublets at $\delta$ 42·33 ($^1J_{CH}$ 127 Hz) and 65·7 ($^1J_{CH}$ 142·6 Hz) can be assigned to C 4a and C 10 respectively. Resonances for C 1 and C 9 occur typically at low fields ($\delta$ 177·3, 180·5) and show close agreement with the related resonances in the

[4] Jackman, L. M., and Sternhell, S., 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry' 2nd Edn (Pergamon Press: New York 1972).

[5] Russell, R. A., Vikingur, E. G., and Warrener, R. N., *Aust. J. Chem.*, 1981, **34**, 131.

model compound (14) which occur at $\delta$ 182·1 and 188·6 respectively.[6] A definitive choice between structures (12) and (13) has not been made. Further chemical support for the gross structure (12) [or (13)] came from its treatment with 1,5-diazabicyclo-[4.3.0]non-5-ene (dbn) in benzene, a reaction which yielded the Grob fragmentation product (17)[7] (Scheme 4).




(12) (17)

**Scheme 4**

The alcohol (12), like the initial adduct (7), retains two oxygen atoms on the central ring, but not at the desired anthraquinone level of oxidation. In view of the relative ease with which anthrones oxidize to anthraquinones,[5] it was expected that oxidation of (12) would be readily achieved. In practice, this was not the case, and, of a variety of oxidants, only the Corey–Fleet reagent,[8] chromium trioxide in the presence of 3,5-dimethylpyrazole, gave satisfactory yields (76%) of the anthraquinone (15).

The sequence (4)+(6) → (7) → (12) → (15) constitutes a new approach to anthraquinones, and succeeds in introducing the two C-ring oxygen atoms simultaneously. Furthermore, ring-substituted 1-acetoxyisobenzofurans (see later) would be expected to react regiospecifically with quinone acetals which should lead to regiospecifically substituted anthraquinones.

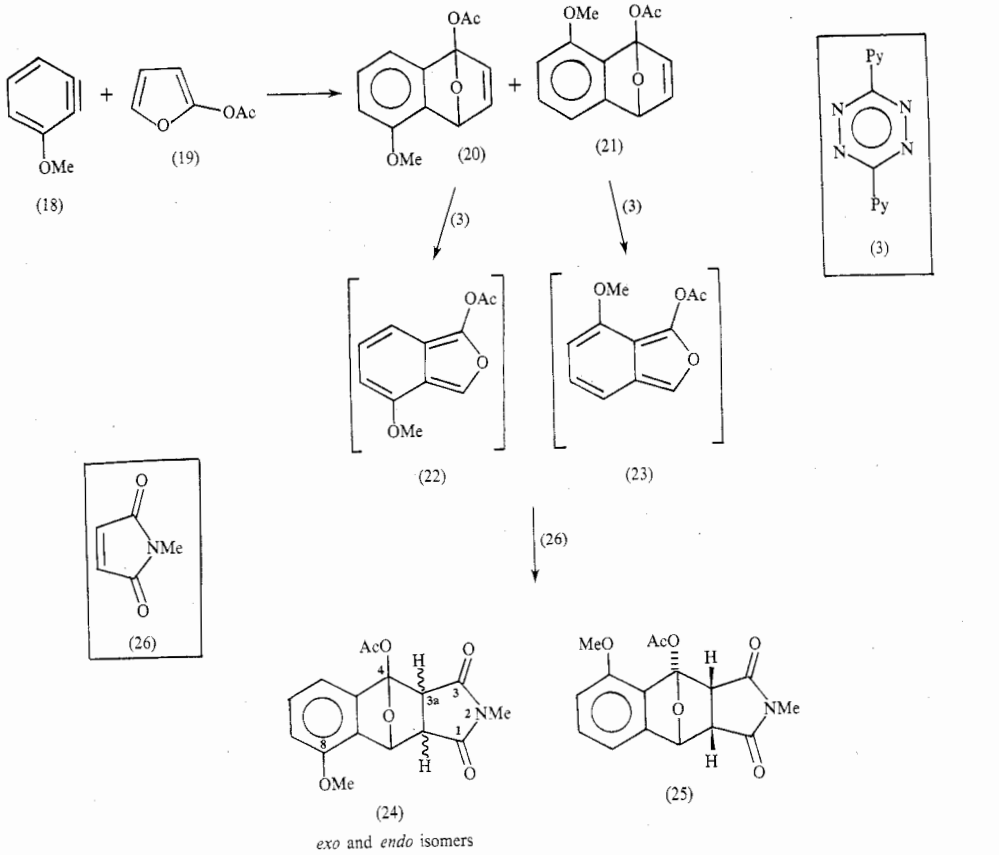
## Further Evaluations

In order to evaluate further the potential of this new method, we sought to prepare the known[9] islandicin precursors (29) and (33). To this end, the ethers (20) and (21) were prepared, as precursors for 4- and 7-methoxy-substituted isobenzofurans (22) and (23), respectively. A mixture of the required ethers (20) and (21) was formed following the addition of 3-methoxybenzyne (18) to 2-acetoxyfuran (19) (Scheme 5), and the ethers (20) and (21) were separated by preparative high-pressure liquid chromatography.

In keeping with previous observations relating to the parent 1-acetoxyisobenzofuran (4), ethers (20) and (21) each reacted with 3,6-di(pyridin-2′-yl)-*s*-tetrazine (3) in the presence of *N*-methylmaleimide (26) to afford respectively the adducts (24) and (25), the former as a pair of stereoisomers. This result indicates that the methoxy-substituted 1-acetoxyisobenzofurans (22) and (23) were generated successfully by the tetrazine route. However, in contrast with (4), these methoxy-substituted 1-acetoxyisobenzofurans failed to react with the quinone acetals (27) or (31), and no evidence for the production of adducts (28) or (32) could be detected.

Attempts to enhance the reactivity of (22) and (23) by generating them at higher temperatures from decomposition of tetracyclone adducts of type (34) has not been

[6] Evans, D. A. C., Ph.D. Thesis, Australian National University, 1981.
[7] Grob, C. A., *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 535.
[8] Corey, E. J., and Fleet, G. W. J., *Tetrahedron Lett.*, 1973, 4499.
[9] Russell, R. A., and Warrener, R. N., *J. Chem. Soc., Chem. Commun.*, 1981, 108.


OMe
(18)
OAc
(19)
OAc
OMe
(20)
OMe
OAc
(21)
Py
Py
(3)
(3)
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OAc
OMe
(22)
OMe
OAc
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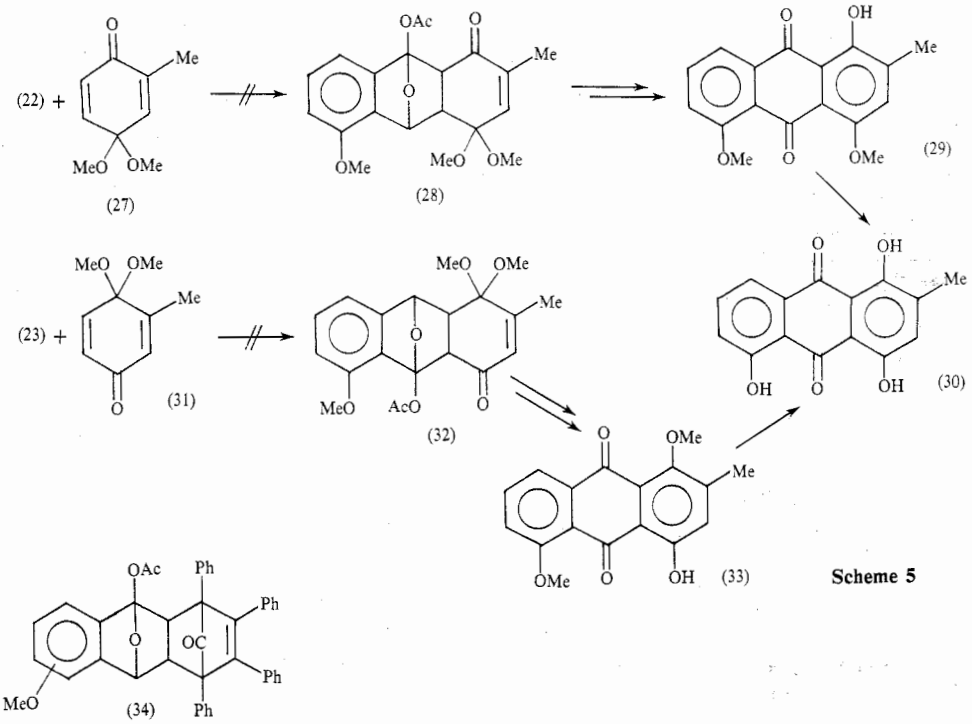
(24)
exo and endo isomers
AcO
MeO
NMe
(25)


(22) +
Me
MeO
OMe
(27)
OAc
Me
OMe
MeO
OMe
(28)
OH
Me
OMe
OMe
(29)
(23) +
MeO
OMe
Me
(31)
MeO
OMe
Me
MeO
AcO
(32)
OH
Me
OH
OH
(30)
OMe
Me
OMe
OH
(33)
OAc
Ph
Ph
Ph
MeO
(34)
Ph

**Scheme 5**

investigated, although this is a known method of inducing cycloadditions to occur with other less-active 1-substituted isobenzofurans.[6]

## Conclusion

It has been shown that an adduct of 1-acetoxyisobenzofuran and *p*-benzoquinone monoacetal can be converted into an anthraquinone in acceptable yield. Whilst this result suggests a promising new synthetic strategy, it has been found, in practice, to have limitations in cases where the isobenzofuran contains deactivating substituents.

## Experimental

*General Methods*

All melting points were determined on a Reichert hot-stage microscope and are uncorrected, whereas boiling points were measured external to the distillation pot in a Buchi Kugelrohr apparatus. Microanalyses were performed by the Australian National University Microanalytical Service. Ultraviolet spectra of solutions in methanol (unless otherwise stated) were recorded with a Unicam SP800 spectrophotometer, matched 5- or 10-mm silica cells being used. Infrared spectra were obtained on either a Perkin–Elmer 283 or a Unicam SP 200G spectrometer as Nujol mulls between two sodium chloride discs.

$^1$H n.m.r. spectra were recorded in $CDCl_3$ (unless otherwise stated) on either a Varian CFT-20 (79·54 MHz), a Jeol JNM-MH-100 (100 MHz) or a Varian EM360A (60 MHz) spectrometer. $^{13}$C n.m.r. spectra were recorded on either a Jeol JNM-FX-60 (15·04 MHz) or a Varian CFT-20 (20 MHz) spectrometer. The chemical shifts are expressed on the appropriate $\delta$ scale relative to tetramethylsilane, which was used as an internal standard. Low-resolution mass spectra were recorded on a Varian MAT CH7 or an A.E.I. MS902 spectrometer. The latter instrument was used for high-resolution mass measurements.

Preparative thin-layer chromatography was performed on either 20 by 100 cm glass plates, with 1-mm layers of silica gel (Merck $HF_{254}$) as adsorbent, or 20 by 20 cm Merck precoated silica (60 $F_{254}$) plates. Column chromatography was performed on either Spence type H activated alumina or May & Baker silica gel. Preparative h.p.l.c. was performed on a Waters Associates 500 liquid chromatograph, PrePAK cartridges being used. Unless otherwise stated, all organic extracts were dried over anhydrous sodium sulfate, and solvents were removed under vacuum.

*2,5-Diacetoxy-2,5-dihydrofuran*

This compound was prepared by a modification of the procedure described by Clauson-Kaus *et al.*[10] Anhydrous potassium acetate (205 g, 2·09 mol) was dissolved in a hot mixture of acetic anhydride (600 ml) and acetic acid (400 ml), and cooled with vigorous stirring to $-17°$ ($CCl_4/CO_2$). Bromine (160 g, 51·9 ml, 2 mol) was added and the mixture maintained at $-17°$ until homogeneous. Furan (80 ml, 1·10 mol) was added and the mixture stirred at $-17°$ until the colour due to bromine was discharged. The mixture was warmed to 0°, maintained at this temperature for 30 min, heated to 80° for 10 min, cooled to room temperature, and filtered to remove potassium bromide. The precipitate was washed with a 10% solution of acetic anhydride in acetic acid, and washings were combined with the filtrate. The solution was freed of solvent under reduced pressure (< 70°/10–15 mm), the residue dissolved in dichloromethane, and washed with saturated sodium bicarbonate. The dried organic phase was freed of solvent to afford crude 2,5-diacetoxy-2,5-dihydrofuran which was used without further purification. Attempts to purify this product by distillation resulted in low yields, and, on occasions, violent and dangerous decomposition occurred. $^1$H n.m.r. $\delta$ 2·13, s, 6H, OAc 6·33, s, 2H, olefinic protons; 6·86 and 7·08, two s, 2H, two isomers OCHOAc.

*2-Acetoxyfuran (19)*

This was prepared from crude 2,5-diacetoxy-2,5-dihydrofuran by the previously reported method,[1,11] b.p. 57–8°/10 mm (lit.[11] 55–58°/10 mm).

[10] Clauson-Kaus, N., Lie, S., and Elming, N., *Acta Chem. Scand.*, 1950, **4**, 1233.
[11] Cava, M. P., Wilson, C. L., and Williams, C. J., *J. Am. Chem. Soc.*, 1956, **78**, 2303.

*1-Acetoxy-1,4-dihydro-1,4-epoxynaphthalene (2)*

This compound was prepared by the reaction of benzyne with 2-acetoxyfuran as previously described.[1] Large-scale preparations were conveniently purified by preparative h.p.l.c. (silica, 10% ethyl acetate in hexane).

*1-Acetoxy-5-methoxy-1,4-dihydro-1,4-epoxynaphthalene (20) and 1-Acetoxy-8-methoxy-1,4-dihydro-1,4-epoxynaphthalene (21)*

A mixture of these two compounds was prepared by allowing 3-methoxybenzyne, generated from 3-methoxyanthranilic acid,[12] to react with 2-acetoxyfuran according to the method described previously.[1]

The two regioisomers were separated by preparative h.p.l.c. (silica, 10% ethyl acetate in hexane). The more mobile isomer, *1-acetoxy-5-methoxy-1,4-dihydro-1,4-epoxynaphthalene* (20), was purified by short-path distillation, to yield a pale yellow oil, b.p. 145°/0·02 mm (Found: C, 66·9; H, 5·5. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). U.v. $\lambda_{max}$ ($\varepsilon$) 291 (1449), 285 (1575), 223 nm (3699). I.r. $\nu_{max}$ (liquid film) 3095w, 3020w, 2940w, 2840w, 1755s, 1610m, 1480s, 1442w, 1372m, 1292s, 1268s, 1240s, 1205s, 1160m, 1147m, 1980m, 1035s, 990s, 956m, 908w, 887m, 862m, 796w, 777m, 740w, 723w, 712w, 678w $cm^{-1}$. $^1H$ n.m.r. $\delta$ 2·28, s, 3H, OAc; 3·80, s, 3H, $OCH_3$; 5·89, s, 1H, H4; 6·60, dd, $J$ 6·9, 2·2 Hz, 1H, aromatic; 6·87–7·06, m, 4H, aromatic, H2, H3. Mass spectrum $m/z$ 233 (5%), 232 (M, 28) (Found: $M^{+\cdot}$ 232·0740. $C_{13}H_{12}O_4$ requires $M^{+\cdot}$ 232·0736), 216 (6), 191 (13), 190 (100), 189 (13), 175 (300), 174 (24), 173 (5), 172 (5), 164 (130), 163 (9), 162 (24), 161 (30), 160 (9), 159 (9), 149 (5), 147 (11), 146 (5), 145 (9), 144 (5), 135 (7), 131 (15), 119 (5), 118 (6), 115 (15), 103 (7), 102 (7), 77 (7), 76 (5), 75 (95), 43 (100); all other peaks less than 5%. *1-Acetoxy-8-methoxy-1,4-dihydro-1,4-epoxynaphthalene* (21), a pale yellow oil, was purified by Kugelrohr distillation, b.p. 150°/0·02 mm (Found: C, 67·1; H, 5·3. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). U.v. $\lambda_{max}$ ($\varepsilon$) 291 (1331), 285 (1388), 240 infl. (850), 223 nm (4134). I.r. $\nu_{max}$ (liquid film) 3100w, 3010w, 2940w, 2840w, 1762s, 1614s, 1604s, 1480s, 1440m, 1370m, 1294s, 1266s, 1208s, 1124m, 1082m, 1034s, 1010m, 987s, 960s, 921m, 880m, 815w, 794m, 784m, 739m, 721m, 677w $cm^{-1}$. $^1H$ n.m.r. $\delta$ 2·25, s, 3H, OAc; 3·78, s, 3H, $OCH_3$; 5·63, s, 1H, H4; 6·60, dd, $J$ 7·6, 1·5 Hz, 1H, aromatic; 6·88–7·09, m, 4H, H2, H3, aromatic. Mass spectrum $m/z$ 233 (5%), 232 (M, 27) (Found: $M^{+\cdot}$ 232·0731. $C_{13}H_{12}O_4$ requires $M^{+\cdot}$ 232·0736), 216 (5), 192 (13), 191 (100), 190 (10), 189 (5), 177 (5), 176 (36), 175 (24), 174 (7), 173 (35), 165 (27), 164 (6), 163 (5), 162 (15), 160 (8), 150 (7), 148 (12), 147 (7), 146 (14), 136 (6), 132 (13), 131 (6), 117 (5), 115 (18), 104 (8), 103 (8), 85 (5), 83 (7), 77 (8), 76 (6), 43 (62); all other peaks less than 5%.

*(4aα,9β,9aα,10α)-9-Acetoxy-4,4-dimethoxy-4a,9,9a,10-tetrahydro-9,10-epoxyanthracen-1(4H)-one (7)*

1-Acetoxy-1,4-dihydro-1,4-epoxynaphthalene (452 mg, 2·24 mmol) and 4,4-dimethoxycyclohexa-2,5-dienone (359 mg, 2·33 mmol) were stirred together in chloroform (10 ml). 3,6-Di(pyridin-2′-yl)-*s*-tetrazine (631 mg, 2·67 mmol) was added and the mixture warmed at 70° for 1 h. The solution was cooled, washed with 5% hydrochloric acid, dried and evaporated to afford a yellow oil, which upon trituration with methanol crystallized as a white solid. Recrystallization from methanol gave the *adduct* (7) (282 mg, 38%) as colourless needles, m.p. 137–139° (Found: C, 65·3; H, 5·5. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%). U.v. $\lambda_{max}$ ($\varepsilon$) 223 (3978), 260 infl. nm (868). I.r. $\nu_{max}$ 1783s, 1680s, 1353m, 1300m, 1274w, 1244m, 1194s, 1152s, 1140s, 1115s, 1095m, 1064m, 1042s, 1000m, 991m, 966s, 946m, 935m, 877w, 851w, 795w, 764w $cm^{-1}$. $^1H$ n.m.r. $\delta$ [($D_6$)benzene] 1·72, s, 3H, OAc; 2·64, s, 3H, $OCH_3$; 2·89, s, 3H, $OCH_3$; 3·48, ddd, $J$ 9·5, 4·6, 1·5 Hz, 1H, H4a; 4·19, d, $J$ 9·5 Hz, 1H, H9a; 5·03, d, $J$ 10·5 Hz, 1H, H2; 5·10, d, $J$ 4·6 Hz, 1H, H10; 5·38, dd, $J$ 10·5, 1·5 Hz, 1H, H3; 6·76–7·08, m, 4H, aromatic. Mass spectrum $m/z$ 330 (M, 11%) (Found: $M^{+\cdot}$ 330·1102. $C_{18}H_{18}O_6$ requires $M^{+\cdot}$ 330·1103), 284 (7), 283 (37), 282 (7), 277 (5), 276 (7), 275 (12), 242 (6), 241 (9), 211 (7), 197 (9), 176 (6), 151 (8), 150 (75), 135 (7), 134 (62), 133 (100), 128 (5), 124 (28), 123 (16), 115 (5), 113 (5), 108 (5), 105 (20), 77 (14); all other peaks less than 10%.

*(4aα,10α)-1,10-Dihydroxy-4,4-dimethoxy-4a,10-dihydroanthracen-9(4H)-one (12)*

The adduct (7) (31 mg, 0·10 mmol), dissolved in methanol (1 ml), was added to a solution of sodium (40 mg, 174 mmol) in methanol (5 ml) at −20° ($CCl_4/CO_2$) and allowed to stir for 5 min.

[12] Warrener, R. N., Russell, R. A., and Marcuccio, S., *Aust. J. Chem.*, 1980, **33**, 2777.

The solution was acidified with dilute acetic acid, and extracted with dichloromethane. The extract was dried and freed of solvent to afford *alcohol* (12) (23 mg, 85%) which crystallized from methanol as pale yellow plates, m.p. 121–122° (Found: C, 66·5; H, 5·6. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). U.v. $\lambda_{max}$ ($\varepsilon$) 238 (9264), 262 infl. (8621), 310 (3210), 377 nm (11373). I.r. $\nu_{max}$ 3513m, 1613s, 1563s, 1346w, 1320w, 1268w, 1217m, 1196w, 1146m, 1116s, 1080m, 1060s, 1030s, 983m, 943m, 831m, 829w, 783s, 745m, 720m, 700w $cm^{-1}$. $^1H$ n.m.r. $\delta$ 3·35, d, obscured, 1H, H4a; 3·43, s, 1H, $OCH_3$; 3·45, s, 1H, $OCH_3$; 4·01, s, 1H, OH; 5·48, d, $J$ 11·3 Hz, 1H, H10; 6·45, d, $J$ 10·5 Hz, 1H, H2 or H3; 6·70, d, $J$ 10·5 Hz, 1H, H3 or H2; 7·24–8·13, m, 4H, aromatic; 15·70, s, 1H, enolic OH. $^1H$ n.m.r. $\delta$ [($D_6$)benzene] 2·78, s, 3H, $OCH_3$; 2·94, s, 3H, $OCH_3$; 3·01, d, obscured, 1H, H4a; 5·57, d, $J$ 12·6 Hz, 1H, H10; 5·73, d, $J$ 10·5 Hz, 1H, H2 or H3; 6·04, d, $J$ 10·5, 1H, H3 or H2; 7·04–7·37, m, obscured by solvent, aromatic; 8·00–8·15, m, 2H, aromatic; 16·41, s, 1H, enolic OH. Mass spectrum $m/z$ 288 (M, 20%), (Found: $M^{+\cdot}$ 288·1005. $C_{16}H_{16}O_5$ requires $M^{+\cdot}$ 288·0998), 263 (5), 262 (20), 242 (7), 240 (9), 228 (20), 227 (8), 214 (7), 212 (11), 198 (10), 168 (6), 155 (5), 154 (15), 139 (15), 133 (19), 128 (100), 127 (8), 124 (13), 123 (100), 115 (5), 113 (15), 110 (10), 109 (6), 105 (21), 102 (6), 101 (55), 99 (5), 95 (33), 88 (7), 86 (40), 85 (8), 84 (59), 81 (5), 80 (7), 79 (6), 77 (17), 76 (5), 69 (6), 65 (9), 64 (6), 63 (7), 59 (9), 57 (5), 55 (15), 54 (11), 53 (11), 52 (12), 51 (14), 50 (5), 49 (12), 47 (17), 45 (8), 43 (10), 41 (20); all other peaks less than 5%.

The residue from the mother liquors was chromatographed on alumina by using chloroform/petroleum as eluent to afford the *phthalide* (10) (3 mg) as colourless crystals, m.p. 111–113° (Found: C, 66·3; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·6; H, 5·6%). $^1H$ n.m.r. $\delta$ 2·29, d, $J$ 7·0 Hz, 2H, H6′; 3·18, obscured dt, $J$ 7·0, 3·0 Hz, 1H, H1′; 3·42, s, 3H, $OCH_3$; 3·50, s, 3H, $OCH_3$; 5·85, d, $J$ 3·0 Hz, 1H, H3; 6·11, d, $J$ 10·5 Hz, 1H, H3′ or H4′: 6·95, d, $J$ 10·5 Hz, 1H, H4′ or H3′; 7·64–7·46, m, 3H, aromatic; 7·94–7·83, m, 1H, aromatic. Mass spectrum $m/z$ 288 (M, <1%) (Found: $M^{+\cdot}$ 288·1025. $C_{16}H_{16}O_5$ requires $M^{+\cdot}$ 288·1024), 260 (9), 257 (5), 256 (7), 214 (5), 155 (14), 134 (11), 133 (100), 128 (41), 127 (96), 124 (6), 115 (6), 114 (8), 113 (9), 105 (18), 104 (5), 99 (12), 96 (7), 95 (5), 81 (7), 77 (25), 76 (7), 59 (15), 55 (1), 53 (12), 51 (14), 50 (15), 41 (10); all other peaks less than 5%.

*3-(2′,2′-Dimethoxy-5′-oxocyclohex-3′-enyl)isobenzofuran-1(3*H*)-one (10)*

A solution of diisopropylamine (0·3 ml, 2·3 mmol) in anhydrous tetrahydrofuran was cooled to −80° and treated with a solution of butyllithium in hexane (1·5 ml, 1·5 M; 2·3 mmol). A solution of isobenzofuran-1(3*H*)-one (268 mg, 2 mmol) in tetrahydrofuran was added dropwise, and the solution maintained at −80° for 10 min to allow complete formation of the anion (16). The resulting yellow suspension was treated with a solution of 4,4-dimethoxycyclohexa-2,5-dienone (6) (308 mg, 2 mmol) in tetrahydrofuran (2 ml), and the mixture stirred at −80° for 20 min. The suspension was warmed to −60°, and treated with methanol (5 ml) followed by dilute sulfuric acid (10 drops, 5%). After warming to room temperature, the solvent was removed and the residue partitioned between water and ether. The dried ethereal phase was freed of solvent to afford a yellow oil which crystallized on trituration with cold ether. The resulting solid was recrystallized (ether/hexane) to afford the product (10) (200 mg, 35%), identical with a sample prepared by the method described above.

*2-(2′-Hydroxy-5′-methoxybenzoyl)benzaldehyde (17)*

The alcohol (12) (19 mg, 0·08 mmol), dissolved in benzene (0·3 ml), was treated with 2 drops of 1,5-diazabicyclo[4.3.0]non-5-ene and allowed to stand for 3 days. The solution was diluted with chloroform, washed with 5% hydrochloric acid, dried and freed of solvent. The residue was chromatographed on a short column of Florosil, with chloroform as eluent, to afford the impure *aldehyde* (17) (11 mg, 61%) as a yellow oil which was further purified by short-path distillation, b.p. 250°/0·05 mm. $^1H$ n.m.r. $\delta$ 3·60, s, 3H, $OCH_3$; 6·59, d, $J$ 2·5 Hz, 1H, aromatic; 7·12–6·95, m, 3H, aromatic; 7·72–7·42, m, 3H, aromatic; 8·09–7·98, m, 1H, aromatic; 10·01, s, 1H, aldehyde; 11·54, s, 1H, OH. Mass spectrum $m/z$ 257 (8%), 256 (M, 42) (Found: $M^{+\cdot}$ 256·0736. $C_{15}H_{12}O_4$ requires $M^{+\cdot}$ 256·0736), 255 (6), 240 (6), 239 (20), 227 (15), 225 (14), 224 (10), 212 (7), 211 (31), 210 (9), 197 (12), 168 (7), 167 (5), 162 (10), 151 (10), 150 (77), 149 (22), 139 (6), 133 (10), 105 (12), 104 (7), 86 (11), 84 (18), 77 (13), 51 (6), 47 (100), 45 (7), 43 (55), 41 (12); all other peaks less than 5%.

*1-Hydroxy-4-methoxyanthracene-9,10-dione (15)*

3,5-Dimethylpyrazole (85 mg, 0·88 mmol) was added to a suspension of chromium trioxide (84 mg, 0·84 mmol) in dichloromethane (1 ml), and the mixture stirred under an atmosphere of

nitrogen for 15 min. To the resulting dark red solution was added the alcohol (12) (49 mg, 0·17 mmol), dissolved in dichloromethane (1 ml). The solution was refluxed for 5 h, cooled and chromatographed on a column of silica to afford the *product* (15) (32 mg, 76%) as an orange solid, m.p. 160–163°, from methanol (lit.[13] 167–168°), which was identical by $^1$H n.m.r. spectroscopy with an authentic sample.

*4-Acetoxy-8-methoxy-2-methyl-3a,4,9,9a-tetrahydro-4,9-epoxy-1*H*-benz*[f]*isoindole-1,3*(2H)*-diones* (*24*)

1-Acetoxy-5-methoxy-1,4-dihydro-1,4-epoxynaphthalene (20) (44 mg, 0·19 mmol) and *N*-methylmaleimide (26) (22 mg, 0·20 mmol), dissolved in chloroform (0·3 ml), were treated with 3,6-di-(pyridin-2′-yl)-*s*-tetrazine (3) (49 mg, 0·21 mmol) at 60° for 0·5 h. The solution was washed with 5% hydrochloric acid solution, dried and freed of solvent to afford an isomeric mixture of *endo* and *exo* adducts (*24*) (3 : 1) (40 mg, 65%), which crystallized from methanol as colourless crystals, m.p. 212–213°. $^1$H n.m.r. (major *endo* isomer) $\delta$ 2·31, s, 6H, $CH_3$; 3·84, s, 3H, $OCH_3$; 4·01–3·77, m, 2H, H 9a; 5·88, d, *J* 4·8 Hz, 1H, H 9; 6·73–6·86, m, 2H, aromatic; 7·14–7·33, m, 1H, aromatic. $^1$H n.m.r. (major *endo* isomer) $\delta$ [($D_6$)benzene] 1·65, s, 3H, $CH_3$; 2·07, s, 3H, $CH_3$; 3·12–3·30, m, 2H, H 3a, H 9a; 3·25, s, 3H, $OCH_3$; 3·89, d, *J* 8·5 Hz, 1H, H 9; 5·67, d, *J* 5·8 Hz, 1H, aromatic; 6·22–6·33, m, 1H, aromatic; 6·84–6·93, m, 1H, aromatic. Mass spectrum *m*/*z* 317 (M, <1%) (Found: $M^{+\cdot}$ 317·0898. $C_{16}H_{15}NO_6$ requires $M^{+\cdot}$ 317·0899), 257 (5), 206 (7), 165 (10), 164 (100), 163 (17), 112 (12), 87 (8); all other peaks less than 5%.

*(3aα,4β,9α,9aα)-4-Acetoxy-5-methoxy-2-methyl-3a,4,9,9a-tetrahydro-4,9-epoxy-1*H*-benz*[f]*isoindole-1,3*(2H)*-dione* (*25*)

1-Acetoxy-8-methoxy-1,4-dihydro-1,4-epoxynaphthalene (21) (51 mg, 0·22 mmol) and *N*-methylmaleimide (26) (27 mg, 0·24 mmol), dissolved in chloroform (0·3 ml), were treated with 3,6-di-(pyridin-2′-yl)-*s*-tetrazine (3) (57 mg, 0·24 mmol) at 60° for 0·5 h. The solution was washed with dilute hydrochloric acid (5%), dried and freed of solvent to afford in essentially quantitative yield the *adduct* (25), which crystallized from methanol as colourless crystals, m.p. 197–198° (Found: C, 59·4; H, 4·9; N, 4·0. $C_{16}H_{15}NO_6.0{\cdot}5CH_3OH$ requires C, 59·4; H, 5·1; N, 4·2%). U.v. $\lambda_{max}$ ($\varepsilon$) 280 (1664), 273 (1604), 220 nm (5942). I.r. $\nu_{max}$ 1770s, 1700s, 1612w, 1597m, 1486m, 1304s, 1274s, 1242m, 1209s, 1150s, 1128s, 1086w, 1066w, 1026s, 1006w, 986m, 969s, 943w, 877s, 809w, 776m, 729w, 705w $cm^{-1}$. $^1$H n.m.r. $\delta$ 2·30, s, 3H, $CH_3$; 2·32, s, 3H, $CH_3$; 2·45–3·89, obscured m, 2H, H 3a, H 9a; 3·80, s, 3H, $OCH_3$; 5·65, d, *J* 5·2 Hz, 1H, H 9; 6·70–6·87, m, 2H, aromatic; 7·13–7·32, m, 1H, aromatic. $^1$H n.m.r. $\delta$ [($D_6$)benzene] 1·24, s, 3H, $CH_3$; 1·45m s, 3H, $CH_3$; 2·48–2·79, m, 2H, H 3a, H 9a; 2·66, s, 3H, $OCH_3$; 4·51, d, *J* 5·6 Hz, 1H, H 9; 5·63, d, *J* 8·1 Hz, aromatic; 5·91–6·21, m, 2H, aromatic. Mass spectrum *m*/*z* 317 (M, 2%) (Found: $M^{+\cdot}$ 317·0895. $C_{16}H_{15}NO_6$ requires $M^{+\cdot}$ 317·0899), 275 (5), 206 (10), 165 (11), 164 (100), 163 (15), 149 (7), 112 (7), 77 (8), 57 (7), 55 (5), 43 (31); all other peaks less than 5%.

## Acknowledgments

We acknowledge the financial support of the Australian Research Grants Scheme. One of us (R.A.R.) also acknowledges a Visiting Fellowship at the Australian National University.

Manuscript received 23 December 1983

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