Acid-catalysed Cyclisations: Structures of Novel Products isolated in the Reaction of 2-[3-(2,6-Dimethoxyphenyl)but-2-enyl]-2-methylcyclopentane-1,3-dione with MeOH–HCl

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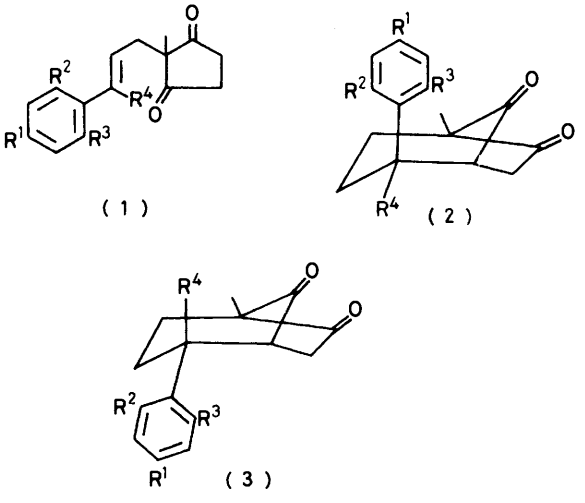
Reaction of the title compound (1a) with anhydrous MeOH–HCl gave 2-*endo*-(2,6-dimethoxyphenyl)-2-*exo*-methyl-5-methylbicyclo[3.2.1]octane-6,8-dione (3a), 1,5,14β-trimethoxy-5,8-seco-6,7-dinorestra-1,3,5(10),9(11)-tetraen-17-one (4), 1,5-dimethoxy-5,8-seco-6,7-dinorestra-1,3,5(10),8,14-pentaen-17-one (5), and 3,4,5,6-tetrahydro-2,7-dimethoxy-3,6-dimethyl-3,2,6-(13-oxopropan[1]yl-[3]ylidene)-2*H*-1-benzoxocin (6). Structures assigned to compounds (3a), (4), and (6) are based on spectral data. The *exo*-tricyclic acetal structure (6) was further confirmed by the analysis of the ^{1}H n.m.r. spectra of the isomeric alcohols (11) and (12), obtained by sodium borohydride reduction of (6).

Kasturi and co-workers [2] have prepared a number of novel C-2 isomeric aryl and alkyl substituted *exo*- and *endo*-5-methylbicyclo[3.2.1]octane-6,8-diones (2) and (3) by reaction of the seco-diones of the type (1) (R^1,R^2,R^3 = H or OMe, R^4 = Me, Et, CH=CH_2, CH_2CH_2OMe, CH=CMe_2, or CH_2-$CHMe_2$) with anhydrous MeOH–HCl. In all the reactions studied so far,[1] it has been found that the *endo*-aryl-*exo*-alkyl isomer (3) predominates over the *exo*-aryl-*endo*-alkyl isomer (2) in the product, in keeping with the expectation that the bulky axial aryl group in (2) would be less stable than the equatorial aryl group in (3). Also, these isomeric bicyclo-[3.2.1]octane-6,8-diones exhibited certain systematic trends in the change of chemical shifts of the bridgehead and the keto-methylene protons with the change in aryl substitution at C-2. To gain a better insight of the mechanism of this reaction and to understand the steric and electronic factors affecting the chemical shifts of the said protons, we attempted the synthesis of the isomeric bicyclic compounds (2a) and (3a) from the corresponding seco-dione (1a) and investigated their n.m.r. spectra. In this paper, we describe the results of this investigation.

The reaction of anhydrous MeOH–HCl with the seco-dione (1a) [3] gave a mixture which could be separated into four fractions. The most polar fraction (15%) was the unchanged seco-dione (1a). The major second, fraction (35%) was a mixture of two compounds (A) and (B) which showed two angular methyl signals at δ 1.16 and 1.05 in their n.m.r. spectra, in the ratio 6 : 5; these could be separated by careful fractional crystallisation. Compound (A) ($M^{+\cdot}$ 316) possessed a carbonyl function ($\nu_{max.}$ 1 740 cm^{-1}) and one aliphatic methoxy-group in addition to the 2,6-dimethoxyaryl group (n.m.r.). In the mass spectrum, the presence of an abundant fragment at *m/z* 190, resulting from the loss of a neutral fragment of 126 mass units followed by further loss of a methyl radical to give the base peak at *m/z* 175, is very significant. This ion (*m/z* 190) could only arise from structure (4), by a retro Diels–Alder fragmentation [4] with the loss of a neutral species (9). Further confirmation of this structure (4) was provided by the ^{13}C n.m.r. spectrum, in particular the signal for C-14 at δ 82.59 p.p.m. (*vide* Table 1). The 14-methoxy-group in the methoxy-ketone (4) is tentatively assigned [5–7] the β-configuration on the basis of the chemical shift of the angular methyl signal (δ 1.15).

The spectral data of compound (B) were similar to those of the isomeric *exo* and *endo* bicyclic compounds reported [1,2] earlier. Structure (3a) for compound (B) was confirmed by *X*-ray analysis.†



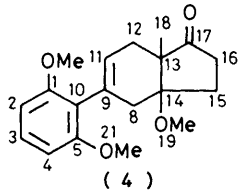
a ; R^1 = H, R^2 = R^3 = OMe, R^4 = Me

The third fraction (4%) was shown to be the extra-pentaenone (5) by comparison with an authentic sample.[3]

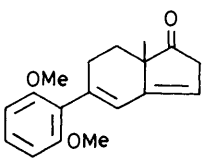
The least polar, fourth fraction (2.5% $M^{+\cdot}$ 302, $\nu_{max.}$ 1 740 cm^{-1}) showed the presence of two methyl singlets (δ 1.03 and 1.56), one aliphatic methoxy- (3.32) and only one aromatic methoxy-group (3.79) in its n.m.r. spectrum. The ^{13}C n.m.r. spectrum (*vide* Table 1) indicated the dissymmetric substitution on the aromatic ring. The appearance of the two low-field aromatic carbon singlets at δ 156.28 and 159.85 p.p.m. were indicative of the attachment of these carbons to oxygen atoms. One of them was a methoxy-substituent (^{1}H n.m.r.) while the other was involved in the cyclisation with the ketonic function. This is also borne out by the low-field quaternary carbon at δ 105.49, attached to two oxygen functions.[8]

On the basis of the above data, two probable structures, (6) and (7) were considered for this compound. The involvement of an 8-ketone [for (6)] or 6-ketone [for (7)] would be re-

† The results of the *X*-ray crystal structure analysis, carried out by K. Venkatesan and co-workers, will be published later.



(4)



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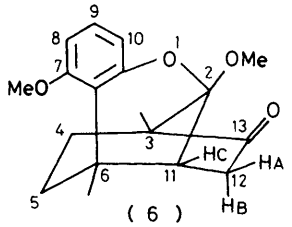
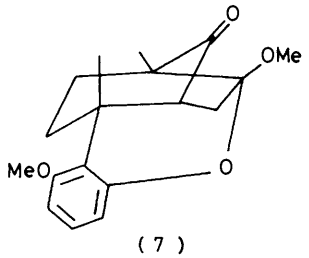
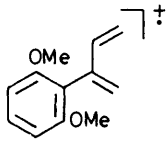


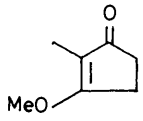
(6)



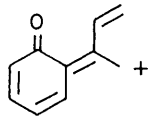
(7)



(8)
m/z 190



(9)
m/z 126



(10)
m/z 175

Table 1. ^{13}C Chemical shifts of compounds (4), (6), (11), and (12)

	Compound			
Atom	(4)	(6)	(11)	(12)
C-1	157.98 (s) [a]	105.49 (s)	107.05 (s)	107.05 (s)
C-2	104.50 (d)			
C-3	128.25 (d)	156.28 (s)	156.40 (s)	156.00 (s)
C-4	104.50 (d)	117.50 (s)	117.40 (s)	118.00 (s)
C-5	157.98 (s)	38.44 (s)	38.19 (s)	39.15 (s)
C-6		31.40 [b] (t)	31.25 [b] (t)	29.05 [b] (t)
C-7		31.96 [b] (t)	33.14 [b] (t)	32.12 [b] (t)
C-8	32.70 [b] (t)	55.46 (s)	49.10 (s)	49.14 (s)
C-9	129.12 (s)	38.87 (d)	40.64 (d)	40.64 (d)
C-10	121.15 (s)	38.22 (t)	35.40 (t)	33.67 [b] (t)
C-11	121.83 (d)	215.61 (s)	74.74 (d)	75.11 (d)
C-12	33.35 [b] (t)	158.85 (s)	159.20 (s)	158.94 (s)
C-13	51.61 (s)	104.47 (d)	104.22 (d)	104.61 (d)
C-14	82.59 (s)	128.16 (d)	127.78 (d)	127.63 (d)
C-15	24.24 (t)	109.06 (d)	108.90 (d)	108.97 (d)
C-16	34.28 [b] (t)	48.64 (q)	48.20 (q)	48.61 (q)
C-17	219.36 (s)	24.95 (q)	24.25 (q)	24.30 (q)
C-18	13.45 (q)	12.06 (q)	13.55 (q)	16.31 (q)
C-19	49.01 (q)	55.46 (q)	55.46 (q)	55.49 (q)
C-20 and C-21	56.11 (q)			

[a] Letter in parentheses indicates the nature of signal. [b] Assignments could be interchanged.

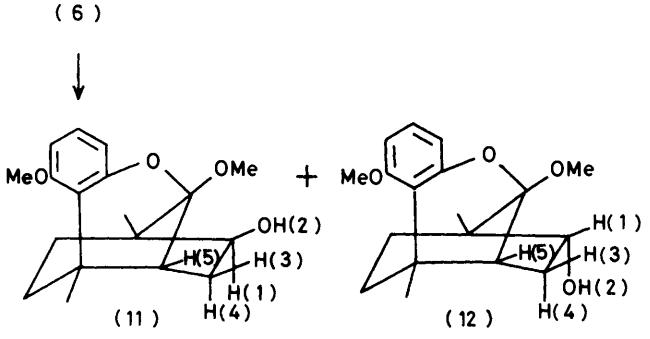
flected in the chemical-shift value of the bridgehead or the ketomethylene protons. The appearance of a two proton multiplet around δ 2.45, as observed in other bicyclic compounds,[2] indicates that the two ketomethylene protons were not affected, while the bridgehead proton was considerably shielded (δ 2.50) compared to that in the starting material (δ 3.80—4.06). This clearly established that the 8-keto-group was involved in the acetal formation. Hence, structure (6) was tentatively assigned for this tricyclic acetal. Further confirmation of this assignment was obtained from the sodium borohydride reduction of the acetal (6) which gave two isomeric alcohols (11) and (12) (Scheme 1). From the chemical shifts and multiplicity of the α-proton (1-H), the configuration of the hydroxy-groups in the two isomers could be deduced [9-11] (*vide* Table 2). Furthermore, it can be seen from Table 2 that the chemical shifts of the ketomethylene protons in the epimeric alcohols (11) and (12) are altered, while that of the bridgehead proton remains unchanged. On this basis, only structure (6) can be assigned to the tricyclic acetal.

The major products obtained in the reaction of MeOH–HCl with compound (1a) were the normal cyclisation products (4) and (5) rather than the bridged systems (3a) and (6). The two *o*-methoxy-substituents on the aromatic ring evidently caused steric hindrance to the pathway (a) leading to the bicyclic

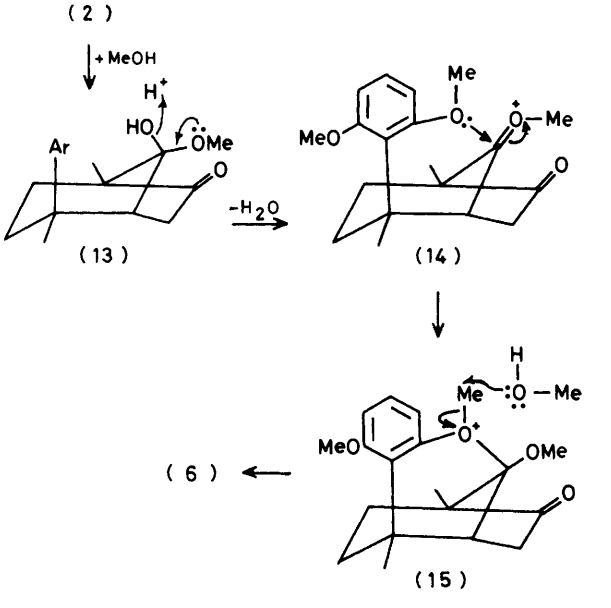
Table 2. Chemical shift and coupling constants of selected protons 1- to 5-H in the *exo* and *endo* tricyclic alcohols (11) and (12) [a]

	Chemical shift in δ (p.p.m.)		Coupling constants (Hz)									
			(11) [b]					(12) [b]				
Proton	(11)	(12)	J_{12}	J_{13}	J_{14}	J_{34}	J_{35}	J_{12}	J_{13}	J_{14}	J_{34}	J_{35}
1-H	3.56	4.08	12.50 [c]	2.94	8.09				10.29	3.31		
2-H	2.53		12.50									
3-H	1.58	2.24		2.94		15.07	7.35		10.29		14.52	7.35
4-H	2.45	1.66			8.09	15.07				3.31	14.52	
5-H	2.14	2.06					7.35					7.35

[a] Chemical shifts and coupling constants of 1- to 5-H inclusive were obtained by first-order analysis. [b] J_{45} = 0 Hz in both alcohols (11) and (12) (see ref. 11). [c] See ref. 6, p. 299.



Scheme 1.



Scheme 2.

(3a) + (6) ← enol addition (path a) — (1a) — normal cyclisation (path b) → (4) + (5)

compounds, rendering the competing cyclisation pathway (b) more feasible. Although some amount of the *endo* bicyclic compound (3a) was isolated, no *exo* bicyclic compound (2a) could be traced in the reaction mixture. The formation of the *exo* tricyclic acetal (6), however, was observed only in this case. Probably, the *exo*-isomer (2a), formed in small quantities, gave rise to this compound (6) by a facile neighbouring-group participation to release the excessive buttressing effect as shown in Scheme 2.*

Experimental

All m.p.s are uncorrected. U.v. spectra were determined for solutions in 95% ethanol using a Shimadzu double beam u.v. spectrophotometer. I.r. spectra (Nujol) were recorded with a Perkin-Elmer 397 spectrophotometer. ^{1}H N.m.r. spectra ($CDCl_3$) were taken on a Brüker WH 270 FT n.m.r. spectrometer and ^{13}C n.m.r. spectra ($CDCl_3$–$CHCl_3$) were recorded on the same instrument operating at 67.89 MHz. Chemical shifts (both ^{1}H and ^{13}C) are quoted in δ values (p.p.m.) relative to Me_4Si as internal standard.

Reaction of 2-[3-(2,6-*Dimethoxyphenyl*)*but*-2-*enyl*]-2-*methylcyclopentane*-1,3-*dione* (1a) *with Anhydrous* MeOH–HCl.—To a solution of the seco-dione (1a) (3.70 g) in anhydrous methanol (45 ml) was added anhydrous methanol (40 ml) saturated with dry hydrogen chloride and the mixture was left at room temperature for 4 h. The methanol was then removed under reduced pressure and the residue was extracted with diethyl ether. The ether extract was washed successively with water, aqueous sodium hydrogen carbonate, water, and dried (Na_2SO_4). The residue obtained after removal of the solvent was subjected to column chromatography over neutral alumina (70 g), followed by preparative layer chromatography, and separated into four fractions.

Fraction 1. The most polar fraction (0.53 g) was the unchanged seco-dione (1a).

Fraction 2. The second fraction (1,58 g) afforded, on fractional crystallisation from ethanol–hexane, 1,5,14β-*trimethoxy*-5,8-*seco*-6,7-*dinorestra*-1,3,5 (10), 9(11)-*tetraen*-17-*one* (4), m.p. 130—132 °C; $\nu_{max.}$ 1 740 cm^{-1}; $\lambda_{max.}$ 218 (ε 17 650) and 278 nm (1 900); δ 1.15 (3 H, s, CH_3), 1.90—2.50 (8 H, m), 3.18 (3 H, s, aliphatic OCH_3), 3.78 (6 H, s, 2 × $ArOCH_3$), 5.41 (1 H, dd, *J* 2.21, 8.82 Hz, vinylic H), 6.57 (2 H, d, J_{ortho} 8.09 Hz, ArH), and 7.20 (1 H, t, J_{ortho} 8.09 Hz, ArH); *m*/*z* 316 ($M^{+\cdot}$, 45%), 190 ($M^{+\cdot}$ − $C_7H_{10}O_2$, 60) and 175 [(8) − CH_3, 100] (Found: C, 72.05; H, 7.9. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%).

After fractional crystallisation, the remaining compound was purified by repeated short-path distillation [200 °C at 2 mmHg (bath temperature)] followed by crystallisation from hexane–benzene to give 2-endo-(2,6-*dimethoxyphenyl*)-2-exo-*methyl*-5-*methylbicyclo*[3.2.1]*octane*-6,8-*dione* (3a), m.p. 114—115 °C; $\nu_{max.}$ 1 765 and 1 728 cm^{-1}; δ 1.07 (3 H, s, CH_3), 1.49 (3 H, s, CH_3), 1.87—1.95 (2 H, m), 2.19—2.32 (1 H, m),

* The authors wish to thank the referee for suggesting a modification of the earlier mechanism.

2.54—2.59 (2 H, m, $COCH_2$), 2.64—2.70 (1 H, m), 3.77 (6 H, s, 2 × $ArOCH_3$), 4.06 (1 H, d, J 5.28 Hz), 6.57 (2 H, d, J_{ortho} 8.09 Hz, ArH), and 7.17 (1 H, t, J_{ortho} 8.09 Hz, ArH); m/z 302 ($M^{+\cdot}$, 6%), 191 ($M^{+\cdot} - C_6H_7O_2$, 100), 163 (87) and 149 (70) (Found: C, 71.2; H, 7.0. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%).

Fraction 3. The third fraction (0.12 g) afforded on crystallisation from hexane–benzene, light orange crystals of 1,5-*dimethoxy*-5,8-*seco*-6,7-*dinorestra*-1,3,5(10),8,14-*pentaen*-17-*one* (5), m.p. 120—121 °C (lit.,[3] m.p. 120 °C; m/z 284 ($M^{+\cdot}$, 25%) (Found: C, 76.3; H, 7.2. Calc. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09%).

Fraction 4. The least polar fourth fraction afforded 3,4,5,6-*tetrahydro*-2,7-*dimethoxy*-3,6-*dimethyl*-3,2,6-(13-*oxopropan*-[1]*yl*[3]*ylidene*)-2H-1-*benzoxocin* (6) (0.09 g) readily on crystallisation from hexane–benzene, m.p. 170 °C; $\nu_{max.}$ 1 740, 1 605, and 1 590 cm^{-1}; δ 1.03 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 1.30—1.72 (4 H, m), 2.42—2.53 (3 H, ABC multiplet, $COCH_2$-CH), 3.32 (3 H, s, aliphatic OCH_3), 3.79 (3 H, s, $ArOCH_3$), 6.49 (1 H, d, J_{ortho} 8.82 Hz, ArH), 6.65 (1 H, d, J_{ortho} 8.82 Hz, ArH), and 7.13 (1 H, t, J_{ortho} 8.82 Hz, ArH); m/z 302 ($M^{+\cdot}$ 100%), 287 ($M^{+\cdot} - CH_3$, 40), and 85 (80) (Found: C, 71.6; H, 7.2. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%).

$NaBH_4$ *Reduction of the* exo-*Tricyclic Acetal* (6).—A solution of the *exo*-tricyclic acetal (6) (0.12 g) in methanol (20 ml) was treated with $NaBH_4$ in portions with stirring at 0 °C during 30 min. The mixture, after being stirred at room temperature for a further 4 h was diluted with cold water. The product was extracted with diethyl ether and the ether extract was washed with water and dried (Na_2SO_4). The residue obtained after removal of the solvent was subject to preparative layer chromatography ($CHCl_3$ as eluant) and separated into two fractions.

Fraction 1 (less polar; 0.046 g), on crystallisation from hexane–benzene, afforded 3,4,5,6-*tetrahydro*-2,7-*dimethoxy*-3,6-*dimethyl*-3,2,6-(13-exo-*hydroxypropan*[1]*yl*[3]*ylidene*)-2H-1-*benzoxocin* (11), m.p. 116 °C; $\nu_{max.}$ 3 580, 3 480sh (OH),[10d,j,12] 1 605 and 1 590 cm^{-1}; δ 1.04 (3 H, s, CH_3), 1.46 (3 H, s, CH_3), 1.15—1.66 (5 H, m), 2.14 (1 H, d, J 7.35 Hz), 2.45 (1 H, dd), 2.53 (1 H, d, J 12.50 Hz, OH, exchangeable with D_2O), 3.32 (3 H, s, aliphatic OCH_3), 3.56 (1 H, sept.), 3.77 (3 H, s, $ArOCH_3$), 6.45 (1 H, dd, J_{meta} 1.10 Hz, J_{ortho} 8.09 Hz, ArH), 6.60 (1 H, dd, J_{meta} 1.10 Hz, J_{ortho} 8.09 Hz, ArH), and 7.09 (1 H, t, J_{ortho} 8.09 Hz, ArH); m/z 304 ($M^{+\cdot}$, 48%) (Found: C, 70.55; H, 8.2. $C_{18}H_{24}O_4$ requires C, 71.02; H, 7.95%).

Fraction 2 (more polar; 0.064 g) crystallised from hexane–benzene to give 3,4,5,6-*tetrahydro*-2,7-*dimethoxy*-3,6-*dimethyl*-3,2,6-(13-endo-*hydroxypropan*[1]*yl*[3]-*ylidene*)-2H-1-*benzoxocin* (12), m.p. 106—112 °C; $\nu_{max.}$ 3 520sh, 3 240br, 3 340sh,[10d,j,12] 1 605, and 1 590 cm^{-1}; δ 1.00 (3 H, s, CH_3), 1.49 (3 H, s, CH_3), 1.22—1.80 (6 H, m), 2.06 (1 H, d, J 7.35 Hz), 2.18—2.30 (1 H, m), 3.25 (3 H, s, aliphatic OCH_3), 3.77 (3 H, s, $ArOHC_3$), 4.08 (1 H, dd), 6.45 (1 H, dd, J_{meta} 1.10 Hz, J_{ortho} 8.45 Hz, ArH), 6.60 (1 H, dd, J_{meta} 1.10 Hz, J_{ortho} 8.45 Hz, ArH), and 7.08 (1 H, t, J_{ortho} 8.45 Hz, ArH); m/z 304 ($M^{+\cdot}$, 65%) (Found: C, 71.25; H, 7.8. $C_{18}H_{24}O_4$ requires C, 71.02; H, 7.95%).

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