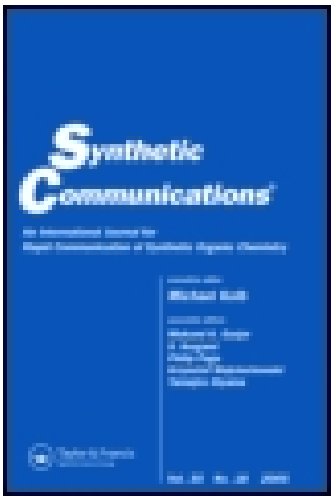

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Synthesis of Spirodiones and Their Structure Determination by X-Ray Crystallography

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SYNTHESIS OF SPIRODIONES AND THEIR STRUCTURE DETERMINATION BY X-RAY CRYSTALLOGRAPHY

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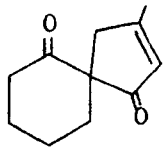
Abstract: A rational synthesis of Spiro bicyclo (5,4) dec-2-ene-3-methyl-1,6-dione (**1**) and Spiro bicyclo (5,5) undec-2-ene-3-methyl-1,7-dione (**2**) from 2-acetyl cycloalkanone is described. Compounds (**1**) and (**2**) have very high potentials as important precursors to many naturally occurring bridged tricyclic compounds. A single crystal X-ray crystallographic study of compound (**2**) was carried out to establish the structure as chemical and spectral methods proved rather inadequate.

Synthesis of natural products via radical induced cyclisation has gained a significant status in the field of synthetic organic chemistry. The versatility of radical generation using tri-n-butyltin hydride and the remarkable degree of stereoselectivity

observed in the subsequent C-C bond formation reaction has made it an attractive approach for a number of natural product synthesis[1].

As a part of our ongoing research programme[2], in tin mediated vinyl radical cyclisation[3], we required the spirodiones **1** and **2** as starting materials and there appears to be no high yield synthesis of these spirodiones available in literature.



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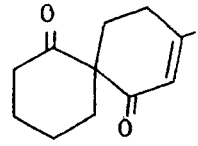
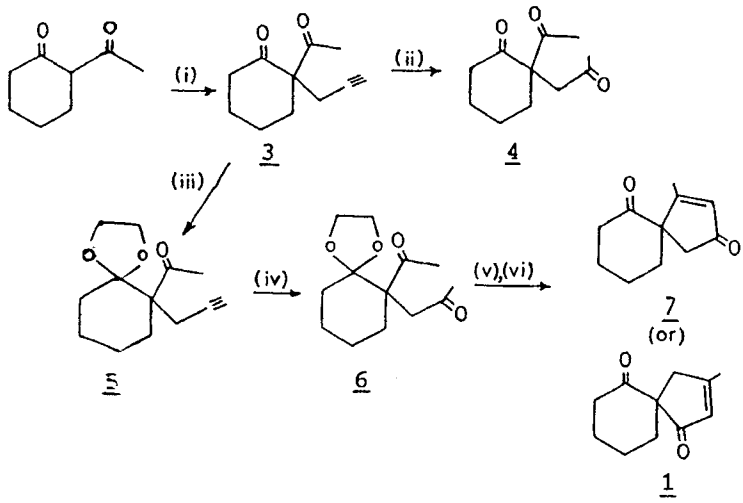


2

Our rational approach to the synthesis of spirodione **1** is detailed in Scheme I.

Alkylation of 2-acetyl cyclohexanone with propargyl bromide gave the C-alkylated product **3** in 85% yield. Hydration of **3** using $HgSO_4/THF/H_2O$ gave the hydrated compound **4** in quantitative yield. Cyclisation of **4** under a variety of conditions was found to give a mixture of compounds in poor yield. In order to carry out preferential spiro-cyclisation, it was felt necessary to protect the ring carbonyl group. Thus ketalisation of **3** using ethylene glycol in the presence of PTS gave the desired ketal **5** in 80% yield.

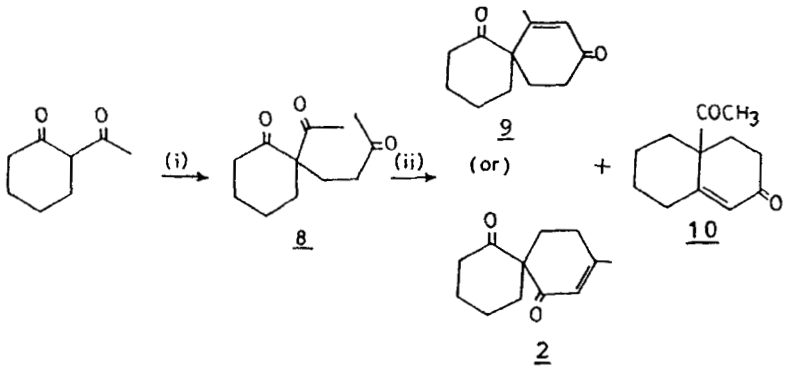


SCHEME 1

Reagents and conditions

i) $tBuO^- K^+/tBuOH/\equiv-CH_2Br, \Delta$, 85%; ii) $HgSO_4/THF/H_2O$; RT., 100%; iii) Ethylene glycol, PTS (cat)/$\phi H, \Delta$, 8hr, 80%; iv) $Hg(OAc)_2$, EtOAc, Δ, 6hr, 60%; v) NaH, Toluene, Δ, 18hr, 80%; vi) 1% HCl, THF, 48hr, RT., 80%

Hydration of the ketal **5** with mercuric acetate in ethyl acetate gave the hydrated product **6**. Cyclisation of **6** using sodium hydride in toluene gave the cyclised compound in 80% yield, which on deketalisation using 1% HCl in THF gave the spirodione. During the cyclisation step, it is possible to envisage the formation of two products. However, a single product was obtained which may have either structure **1** or **7**.



SCHEME II

The homologous spirodione **2** was synthesised as outlined in Scheme II.

Reagents and conditions

i) NaOEt (cat), mvk, EtOH, ϕH, RT., 80%; ii) a. Pyrrolidine, hexane, Δ , 8 hr.; b. NaOACb/HOAc/H_2O, ϕH, Δ , 8hr.

Treatment of 2-acetyl cyclohexanone with mvk in the presence of catalytic amount of sodium ethoxide gave the Michael adduct **8** in 85% yield. Cyclisation of **8** was achievied using pyrrolidine in hexane thereby forming an enamine, followed by hydrolysing it with sodium accetate/acetic acid buffer. Column chromatography of the liquid material and elution with EtOAc : hexane (5 : 95) gave a solid material in 60% yield; m.p.76-77°C, whose structure may be **2** or **9**. Further elution gave the known bicyclic compound **10** in

10% yield. With the aid of spectral data the structure **9** was assigned to the major cyclised product[5]. Meanwhile Brunner et al.,[6] have studied the cyclisation of trione **8** which is optically active using PTS in benzene and reported formation of compound **2** in 46% yield and its structural assignment was based on spectral data comparision with compound **10**. However, there is no mention about other possible product **9** whose spectral data will agree with the compound **2**.

Spectral data proved inadequate with regards to structural assignment to the spiro compound **1** or **7** and **2** or **9**. Structural proof was sought involving chemical reactions. If the spirodiones were to have the structure **7** and **9**, their corresponding vinyl alcohols would have the feature to undergo a (3,3) sigmatropic rearrangement[7]. In the event, the vinyl alcohols of the spirodiones prepared by standard methods failed to give the rearrangement product either thermally or under base catalysis. From the spectral analysis of the product it was inferred that both the spirodiones should have similarity in structure (i.e., **1** and **2** or **7** and **9**). The establishment of structure of spirodiones by chemical means reveal that both the spirodiones have similarity in their structure and since the spiro (5,5) undecane (n=2) was found to be a crystalline solid, its single crystal X-ray analysis was undertaken. The X-

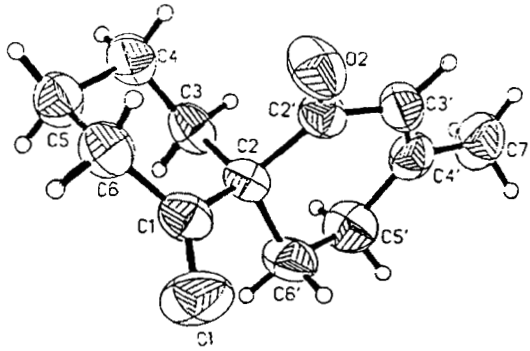


Figure I. ORTEP representation of structure 2.

ray crystallographic data clearly proves the structure as **2** and incidentally the spiro (5,4) decane (n=1) should have the structure **1**. An ORTEP representation of the structure **2** present in the unit cell is shown in Figure I[8].

The spiro (5,5) undecane skeleton **2** has the desired functional groups for further elaboration to naturally occuring compounds (eg. (±) α - Chamigrene[9]).

EXPERIEMENTAL

Preparation of 2-acetyl-2-propargyl cyclohexanone. (3):

A solution of 2-acetylcyclohexanone (28.0g, 0.2 mole) in t-butanol (25 ml) was added to a mixture of potassium t-butoxide (prepared from potassium metal (8.58g, 0.22 mole) in 250 ml of t-butanol) during 30

min. under reflux in nitrogen atmosphere. After stirring for 30 min. at reflux temperature, propargyl bromide (28.5g, 0.24 mole) was added dropwise over a period of 90 min. The resulting mixture was further refluxed for 1 hr. The solution was cooled and the solid potassium bromide was filtered off and from the filtrate t-butanol was removed under reduced pressure. Water (150 ml) was added to the residue and extracted with ether (4 x 50 ml). The ether layer was washed with water, brine, dried over anlayd. $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was distilled under vacuum. b.p. 142°C at 10 mm; Yield: 30.5g (85.5%); IR ($CHCl_3$) ν_{max}: 3300, 2980, 2100, 1700 - 1690 cm^{-1}.

Preparation of 1,4-dioxa-6-acetyl-6-propargyl spiro (4.5) decane. (5):

A 250 ml round bottomed flask was charged with 13.5g (0.0758 mole) of **3**, 9.1 ml (0.163 mole) of ethylene glycol, 15 mg of pyridinium p-toluene sulphonic acid and 100 ml of benzene. The flask was attached to a water separator under reflux condenser, and the mixture was refluxed until the theoretical amount of water (1.3 ml) was collected in the trap. The reaction mixture was washed with saturated sodium bicarbonate solution, water and dried over anhyd. $MgSO_4$. The solvent was removed under low pressure and

the residue was distilled under vacuum. b.p. 140°C at 1 mm; Yield = 13g (77.3%); IR ($CHCl_3$) ν_{max} : 3300, 2800, 2100, 1700 cm^{-1}; ^1H NMR (90 MHz, CCl_4/TMS) δ: 3.85 (br s, $-OCH_2-$, 4H), 2.05 (s, $-CO-CH_3$, 3H), 1.3 - 3.1 (m, methylenes, acetylenic H, 11 H).

Preparation of 1,4-dioxa- 6-acetyl - 6-acetonyl spiro [4.5] decane. (6):

A 100ml round bottomed flask was charged with 6.68g (0.03 mole) of **5**, 14.31g (0.045 mole) of mercuric acetate and 60 ml of ethyl acetate. The solution was refluxed for 6 hr. The solution was cooled and hydrogen sulphide was passed and the precipitated mercuric sulphide was filtered off. The solvent was removed from the filtrate and the residue was extracted with ether (6x25 ml). The ether solution was washed successively with water and dried over anhyd. $MgSO_4$. The solvent was removed and the residue was chromatographed over alumina. Yield = 32 g (60%); IR ($CHCl_3$) ν_{max} : 2950, 1715, 1705 cm^{-1}; ^1H NMR (90MHz, CCl_4/TMS) δ: 3.85 (br s, $-O-CH_2-$, 4H), 3.33 (d, H_{11B}, 1H), 2.58 (d, H_{11A}, 1H), 2.16 (s, $-CO-CH_3$, 3H), 2.02 (s, $-COCH_3$, 3H), 1.16 - 1.8 (m, methylenes, 8H).

Cyclisation of compound (6)

To a stirred suspension of NaH (5.68g, 0.233 mole) in dry toluene (100 ml) under nitrogen was added

diketone **6** (7g, 0.0291 mole) in toluene (50 ml) dropwise under reflux and the resulting mixture was refluxed for 18 hr, cooled to 0°C and carefully acidified with dil. HCl. The layers were separated and the aqueous layer was extracted with ethyl acetate (2x25 ml). The combined organic extracts were washed with brine and dried over anhyd. $MgSO_4$. Removal of the solvent under reduced pressure gave a light yellow oily residue which was purified by chromatography over alumina to give the cyclised product. Yield = 5.2g (80.3%); IR ($CHCl_3$) ν_{max} : 2980, 1690, 1640 cm^{-1}; ^1H NMR (90 MHz, CCl_4/TMS) δ: 5.7 (s, olefinic H, 1H), 3.85 (br s, -O-CH_2, 4H), 2.1 (s, vinylic methyl, 3H), 1.5 - 2.4 (m, methylenes, 10H).

Deketalisation of the cyclised product

A solution of the cyclised ketal 2.08g (0.01 mole) and 10 ml of 10% HCl in 30 ml of THF was stirred at room temperature for 48 hr. Ether was added and the mixture was washed with saturated sodium bicarbonate solution, water and dried over anhyd. $MgSO_4$. Removal of the solvent and column chromatography of the residue over silica gel gave the ketone **1**. Yield = 1.3g (80%); IR ($CHCl_3$) ν_{max}: 2980, 1705, 1690, 1630 cm^{-1}; ^1H NMR: (90MHz, CCl_4/ TMS) δ: 5.5 (s, olefinic H, 1H), 3.49 (d, H_{4A}. 1H), 2.16 (s, vinylic methyl, 3H), 0.83

- 3.0 (m, methylenes & H_{4B}, 9H); Mass spectra: m/z, 178 (M^+) ; Elemental analysis : Calculated : C% 74.13493, H% 7.91705; Found : C% 74.02, H% 7.90.

Preparation of spiro bicyclo (5.5) undec-2-ene-3-methyl-1,7 - dione. (2):

To a stirred solution of NaOEt (cat. amount) in EtOH, 2-acetyl cyclohexanone 20g (0.143 mole) in 100 ml of benzene was added over a period of 45 min. under nitrogen atmosphere. Stirring was continued for 30 min. To the resulting solution, methyl vinyl ketone 11.99 g (0.172 mole) in 100 ml of benzene:ethanol (1:1) was added dropwise and the solution is stirred for an additional 9 hr at room temperature. 50 ml of brine solution was added and the aqueous layer was separated. The organic layer was washed with potassium dihydrogen phosphate solution and dried over anhyd. $MgSO_4$. The solvent was removed under reduced pressure and the crude residue was pure enough to be used as such for cyclisation. Weight obtained = 24g (79.9%); IR ($CHCl_3$) ν_{max}: 1730-1700 cm^{-1}.

A 250 ml round bottomed flask was charged with 2-acetyl-2-(3-oxobutyl) cyclohexanone (24g, 0.119 mole) pyrrolidine (20.8g, 0.179 mole) and hexane (100 ml). The flask was attached to a water separator under reflux condenser, and the mixture was refluxed until no

more water was collected in the trap (6 hr). The excess pyrrolidine and the solvent hexane was removed under reduced pressure. The crude enamine was taken in 100 ml of benzene and hydrolysed using NaOAc - HOAc - H_2O (1:2:2) buffer solution by refluxing for 6 hr. The organic layer was washed with dil. HCl, water, dried over anhyd. $MgSO_4$. Removal of the solvent yielded a viscous brown liquid which was chromatographed over silica gel. On elution with ethylacetate : hexane (5 : 95), the compound **2** was obtained as a white crystalline solid. Yield = 13.2g (60 %); m.p., 76 - 77°C (hexane); IR ($CHCl_3$) ν_{max}: 1705, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ: 1.5096-2.0312(m, methylenes, 6H), 5.7881 (s, olefinic H, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ: 210.837 (s), 198.314 (s), 162.080 (s), 125.273 (d), 58.576 (s), 41.029 (t), 34.957 (t), 30.813 (t), 27.990 (t), 26.943 (t), 23.937 (q), 20.917 (t); Mass spectra : m/z - 192 (M^+); Elemental analysis : Calculated : C% 74.96832, H% 8.38798; Found : C% 74.96, H% 8.39.

Further elution with ethyl acetate : hexane (10 : 90) gave the known bicyclic compound **10**. Yield = 2.2g (10%); m.p., 95-96°C (hexane); IR ($CHCl_3$) ν_{max}:1690, 1675, 1625 cm^{-1} ; ^1H NMR (90 MHz ; CCl_4/TMS) δ: 1.28 - 2.02 (m, methylenes, 6H), 2.14 - 2.52 (m, methylenes, 6H), 2.26 (s, - $COCH_3$, 3H), 5.99 (br s, olefinic H, 1H) ; ^{13}C NMR (72.5 MHz, $CDCl_3$/TMS) δ:

22.99 (t), 25.40 (t), 26.50 (t), 33.33 (t), 33.93 (t), 34.18 (q), 37.17 (t), 55.31 (s), 126.17 (d), 164. 84 (s), 197.92 (s) and 209.82 (s).

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8. Crystal data for **2**. $C_{12}H_{16}O_2$, M = 384.5, Space group PT, a = 6.630 (1), b = 9.073 (2), c = 9.836 (2) A^{o}. α = 90.14 (3), β = 105.14 (3), γ = 92.85 (3), U = 527.34 A^3. D_c = 1.211g cm^{-3}, Z = 2, F (000) = 208.0, $\mu(M_o-K_\alpha)$ = 0.08 MM^{-1}, λ = 0.71069nm. Of 1546 reflections collected, 1255 reflections I> 3 σ (I) were used for calculations. The structure

was solved by direct methods. The hydrogen atoms were located from a fourier map. The full-matrix least squares refinement was completed using anisotropic thermal parameters for all non-hydrogen atoms. The final R was 0.0357 and R_w = 90.0436, where $W = 1/(\sigma^2 (F) + 0.00188 F^2)$. The number of parameters refined were 129 and the goodness of fit is 2.90.

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