A simple synthesis of bis-annulated bicyclo[2.2.2]octenones containing a \( \beta,\gamma \)-enone chromophore and photochemical reactions: a new entry into angular tetraquinane and other polycyclic systems

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Abstract—Synthesis of endotetracyclo[5.5.2.0.2,6,0.8,12]tetradeca-3(4),8(12)-dien-13-one from 5-indanol and photoreactions in singlet and triplet excited state leading to complex polycyclic systems is reported. Crystal structure of 14-spiroepoxy endotetracyclo[5.5.2.0.2,6,0.8,12]tetradeca-3(4),8(12)-dien-13-one is also reported.

1. Introduction

Bridged carbocyclic systems containing a \( \beta,\gamma \)-enone chromophore have proved to be versatile precursors for the synthesis of a variety of carbocyclic arrays because of their unique reactions in both the ground and excited states. 1–3 The reactions in excited states permit a smooth and stereoselective transformation of bridged structure into ring fused system present in a large number of naturally occurring compounds. 2 However, there are some methods for the synthesis of simple bicyclo[2.2.2]octenones 4 and monoaannulated homologue, 5 there are no methods for bis-annulated bicyclo[2.2.2]octenes of type 1 having a \( \beta,\gamma \)-enone chromophore. Recently, the reactive species generated from aromatics such as cyclohexadienone ketals, \( \alpha \)-imido quinones have received greater attention for creation of complex molecular structures. 6, 7 In view of our interest 2 in the chemistry of cyclohexa-2,4-dienones and the continuing interest in the synthesis of angular tetraquinanes 8, 9 we thought to devise a method for the synthesis of bis-annulated bicyclo[2.2.2]octenones of type 1 containing a \( \beta,\gamma \)-enone group and explore its photoreactions. We wish to describe an efficient synthesis of tetracyclic compounds of type 1 from a simple aromatic precursor 5 via cycloaddition of the annulated cyclohexa-2,4-diene 4, and also report photochemical reactions of 1 in triplet and singlet excited state that provides a new stereoselective entry to 2, 3 and other carbocyclic systems (Fig. 1).

2. Results and discussion

The tetracyclic diene 1 was efficiently synthesized from indanol 6 as follows. The hydroxymethyl indanol 5 10 was prepared by controlled hydroxymethylation of commercially available indanol 6 (Scheme 1). Thus, the treatment of 6 with aq. HCHO and NaOH at ambient temperature gave a mixture of mono- and bis-hydroxymethylated products from which hydroxymethyl indanol 5 was obtained in moderate yield after chromatography. Oxidation of 5 in the presence of a freshly cracked cyclopentadiene with aq. sodium meta periodate 11 following a procedure developed in our laboratory, 5 gave the keto-epoxy adduct 8 in excellent yield (83%) as a result of in situ generation of 4 and subsequent interception with cyclopentadiene (Scheme 1). The gross structure of the adduct was deduced from the following spectroscopic data. Thus, the \(^1\)H NMR (400 MHz) spectrum of the adduct exhibited characteristic signals at \( \delta 5.67 \) (m, 1H), \( \delta 5.39 \) (m, 1H) for the olefinic protons of the five-membered ring. Further, characteristic AB pattern for protons of the oxirane methylene group was observed at \( \delta 3.42–3.39 \) (superimposed m, 2H), \( \delta 3.08–3.00 \) (m, 1H), \( \delta 2.62–2.49 \) (m, 3H), \( \delta 2.44–2.32 \) (m, 2H), \( \delta 2.23–2.21 \) (m, 2H).

Keywords: Cycloaddition; Cyclohexa-2,4-diene; Oxa-di-\( \pi \)-methane rearrangement; 1,3-Acyl shift; Photoreaction.
(m, 1H), 2.02–1.87 (m, 3H) for other methine and methylene protons. $^{13}$C NMR spectrum displayed characteristic signals at δ 205.02, and 140.75, 136.64, 133.00, 129.21 for carbonyl carbon and olefinic carbons respectively. Signals due to other carbons were shown at δ 85.95, 53.58, 52.57, 50.44, 44.60, 38.34, 36.89, 35.42, 34.17, 23.69. However, the stereochemical orientation of the oxirane ring was not easily discernible from the spectroscopic data alone and it was difficult to distinguish between 8 and the possible diastereoisomer 9. Hence, X-ray crystal structure determination was undertaken which confirmed the structure 8 for the adduct (Fig. 2).

The adduct 8 was then converted into the chromophoric system 1. Thus, the treatment of 8 with zinc in aqueous methanol containing NH$_4$Cl at ambient temperature gave the β-hydroxy ketone 10 (as a mixture of syn–anti isomers) also in excellent yield (92%). Oxidation of 10 with Jones reagent followed by decarboxylation of the resulting β-ketoacid readily furnished the desired chromophoric system 1 (Scheme 1). It may be worth noting that the tetracyclic compounds of type 1 are not readily accessible otherwise.

After having an efficient access to the tetracyclic chromophoric system 1, we first explored its photochemical reaction in excited singlet (1S) state. In general, the rigid β,γ-enones undergo two unique reactions i.e. a 1,2-acyl shift or oxa-di-π-methane rearrangement on triplet sensitized ($T_1$, π–π$^*$) irradiation and a 1,3-acyl shift upon direct irradiation either via singlet excited state ($S_1$) and/or higher triplet ($T_2$, n–π$^*$) state.$^{1-3}$ The unusual reactivity is a consequence of the electronic interaction between the chromophores that modulates the structure and properties of the excited states. However, the selectivity in the photoreaction also depends on the structure of the chromophoric systems and functional groups in a subtle fashion. Keeping the above in mind, a solution of 1 in dry benzene was irradiated with a mercury vapor lamp (125 W, APP) in a Pyrex immersion well under nitrogen. Chromatography of the photolysate gave the tetracyclic compound 3 (Scheme 2) containing a cyclobutanone ring in a good yield (40%) as a result of 1,3-acyl shift. The structure of the photoproduct was clearly revealed from the spectroscopic data. In order to examine the photoreaction of 1 in triplet excited state, a solution of 1 in dry acetone (both as a solvent and sensitizer) was irradiated with a mercury vapor lamp.

Scheme 1. Reagents/conditions: (i) NaOH, HCHO, 5 (30%), 7 (30%); (ii) aq. NaIO$_4$, CH$_3$CN, cyclopentadiene, 0–5 °C, 83%; (iii) Zn, NH$_4$Cl, aq. MeOH, rt, 92%; (iv) Jones reagent, acetone; (v) aq. THF, Δ, 55% (for iv and v).

Figure 1.

Figure 2. X-ray crystal structure of compound 8.
(125 W, APP) in a Pyrex immersion well \((\lambda > 290 \text{ nm})\) under nitrogen for 1 h. Chromatography of the photolyzate gave the tetracyclic dienone 3, the caged ketone 11 and the polyquinane 2 in 23, 15 and 20\% yields respectively, as a result of 1,3-acyl shift, intramolecular \(\pi^2 + \pi^5\) cycloaddition and oxa-di-\(\pi\)-methane rearrangement. In order to improve the efficiency of the oxa-di-\(\pi\)-methane reaction, we also irradiated a solution of 1 in acetone at 254 nm (16 W mercury vapor lamp APP) in a quartz immersion well for 3 h. Under this condition, the oxa-di-\(\pi\)-methane product 2 was obtained in better yield (35\%), the formation of 1,3-acyl shift product 3 remained unchanged and the caged product 11 was formed to a greater extent (Scheme 2).

The formation of the 1,3-acyl shift product 3 and, especially the caged product 11 during the sensitized irradiation of 1 was rather surprising since other bicyclo[2.2.2]octenones without the substituents at \(\beta,\gamma\)-olefinic carbons undergo highly selective photoreaction.\(^2,^3,^5\) It appears that the unusual behavior of the tetracyclic compound 1 upon sensitized irradiation is due to the presence of the strained five-membered ring across the \(\beta,\gamma\)-olefinic bond which controls the structure and properties (electronic and steric effects) of both the ground and the excited state so as to populate \(T_2\) and \(T_1\) indiscriminately and also sensitize the \(\pi\)-bonds for intramolecular photocycloaddition.

The oxa-di-\(\pi\)-methane rearrangement in 1, although it occurred with moderate efficiency, provided a stereoselective route to angular polyquinanes which are present in many natural products.\(^6,^9\) In order to convert the pentacyclic compound 2 into tetraquinane, selective cleavage of the peripheral cyclopropane bond was required. Though several methods are available,\(^1^2\) radical induced reductive cleavage\(^1^3\) was attempted. Thus, treatment of the pentacyclic compound 2 with tributyltin hydride-AIBN in refluxing benzene furnished the tetraquinane 12 in good yield (65\%) (Scheme 3). The presence of an absorption band at 1737 cm\(^{-1}\) in IR spectrum and a signal at \(\delta 223.15\) in the \(^{13}\text{C}\) spectrum of 12, characteristic of a CO group in five-membered ring, in addition to other spectral data clearly suggested its structure.

In summary, transformation of a readily available aromatic precursor to a new complex tetracyclic system 1 endowed with a \(\beta,\gamma\)-enone chromophore and its photoreaction upon singlet and triplet excited state leading to novel carbocyclic systems is described. An unusual effect of structure on the photoreactivity in the triplet excited state is also presented.

3. Experimental

3.1. General

IR spectra were recorded on Nicolet Impact 400 FT-IR Instrument. UV spectra were recorded on Shimadzu UV 160 or Shimadzu U 260 instrument. \(^1\text{H}\) NMR and \(^{13}\text{C}\) NMR were recorded on Bruker Avance-400 NMR spectrometer, Varian NMR and Varian VXR 300 instruments. Micro-analyses were done on a CEST 1106 instrument and HRMS was done on Q-Tof micro (YA-105) and Brucker Daltonics APEX3 Tesla Mass Spectrometer. Melting points were determined on a Vego apparatus of Buchi type and are uncorrected. All the organic extracts were dried over anhydrous sodium sulphate. Reactions were monitored with thin layer chromatography silica gel and spots were visualized with iodine vapor. Column chromatography was performed using Acme/SRL silica gel (60–120 or 100–200 mesh). The elution was done with petroleum ether (60–80 °C) and ethyl acetate mixtures. The fractions eluted from column were concentrated at reduced pressure on a Buchi-RE 111 rotary evaporator.

3.1.1. 6-Hydroxymethyl-5-indanol (5) and 2,6-dihydroxymethylindanol (7). To a solution of indanol 6 (3.0 g, 22.4 mmol) in water (120 mL), NaOH (0.76 g, 19 mmol) and formaldehyde (2 mL, excess) were added at ambient temperature and the reaction mixture was stirred for 3 h. Then the reaction mixture was neutralized with \(\text{NH}_2\text{Cl}\), at 0 °C and extracted with ethyl acetate (4×50 mL). The
combined organic extract was washed with brine (1 × 20 mL) and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the residue was flash chromatographed. Elution with petroleum ether–ethyl acetate (95:5) first gave the unreacted starting material. Further elution with petroleum ether–ethyl acetate (90:10) furnished the desired compound 5 (1.2 g, 30%) as a colorless solid. Elution with petroleum ether–ethyl acetate (70:30) gave the bis-hydroxymethylated product 7 (1.4 g, 30%) as a colorless crystalline solid.

Data for 5. Mp 104–106 °C. IR νmax: 3434, 1591 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.04 (s, 1H, phenolic-ΟΗ), 6.88 (s, 1H, aromatic proton), 6.76 (s, 1H, aromatic proton), 4.78 (d, J = 3 Hz, 2H, Ar-CH₂-OH), 2.88–2.77 (m, 4H), 2.26 (br m, 1H, CH₂OH), 2.09–2.00 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 154.59, 145.93, 135.55, 123.44, 122.54, 112.44, 64.66, 32.91, 31.90, 25.76. Analysis: Found C, 72.99; H, 7.71; requires C, 73.17; H, 7.31 for C₁₀H₁₅O₂.

Data for 7. Mp 108–110 °C. IR νmax: 3405, 3318, 1610 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 8.08 (s, 1H, phenolic OH), 6.92 (s, 1H), 4.84 (d, J = 3 Hz, 2H, CH₂OH), 4.75 (d, J = 3 Hz, 2H, CH₂-OH), 2.84–2.79 (m, 4H), 2.64 (br m, 1H, OH), 2.52 (br m, 1H, OH), 2.08–2.03 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 153.4, 142.8, 135.3, 124.4, 123.2, 121.5, 63.6, 60.9, 32.1, 31.0, 25.3. HRMS: 217.0848 (M⁺ + Na) C₁₁H₁₄O₂Na requires 217.0841.

3.1.3. 14-Hydroxymenthendotetraacyclo[5.5.2.0²,6.0⁸,1₂]tetradeca-3(4),8(12)-dien-13-one (10). A solution of the adduct 8 (3.0 g, 13.2 mmol) in methanol–water (6:1, 105 mL) was added zinc (activated 18 g, excess) and NH₄Cl (3.3 g, 59 mmol). The reaction mixture was stirred at ambient temperature (30 °C) for 8 h (TLC). It was filtered on a celite bed and washed with ethyl acetate (4×40 mL). The combined organic layer was washed with brine and dried. The solvent was removed under reduced pressure and the residue was chromatographed. Elution with petroleum ether–ethyl acetate (88:12) gave the alcohol 10 (syn–anti mixture) as a colorless liquid (2.8 g, 92%). IR νmax: 3446, 1714 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.63–5.59 (m, 1H), 5.38–5.32 (m, 1H), 3.90–3.80 (m, 1H), 3.70–3.64 (m, 1H), 3.55 (d, J = 7.8 Hz, 1H), 3.30–3.14 (merged m, 3H), 2.97, 2.87 (m, total 1H), 2.80–2.70 (m, 1H), 2.60–2.20 (cluster of m, 6H), 2.0–1.82 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 215.77, 143.85, 135.74, 134.62, 129.53, 62.82, 54.46, 50.85, 50.36, 40.46, 40.43, 38.35, 35.48, 35.09, 33.78, 23.50 (signals due to one isomer). HRMS: C₉₂H₆₈O₂ requires 253.1205 (M⁺ + Na). C₁₃H₁₄O₂ requires 253.1199. This was subjected to oxidation and decarboxylation as described below.

3.1.4. endo-Tetraacyclo[5.5.2.0²,6.0⁸,1₂]tetradeca-3(4),8(12)-dien-13-one (1). A solution of the β-keto-alcohol 10 (2.0 g, 8.7 mmol) in acetone (60 mL) was oxidized with freshly prepared Jones' reagent at 0 °C. After completion of reaction (TLC), isopropanol was added to destroy excess oxidant. Acetone was removed in vacuum at ambient temperature and the residue was diluted with water (10 mL) and extracted with dichloromethane (3×25 mL). Combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed and the resulting β-keto-acid was dissolved in THF–water mixture (1:1, 30 mL) and refluxed for 10 h. It was brought to ambient temperature, and the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with ether (3×30 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed and the resulting compound was recrystallized from petroleum ether–ether (98:2) to give the desired product 1 (3.43 g, 83%) as a solid which was recrystallized with petroleum ether–ether-acetate (95:5) to give the pure compound 1 (0.85 g, 55%) as a colorless solid. Mp 70–71 °C. IR (film) νmax: 1723 cm⁻¹. UV (MeOH) λmax: 215 (ε = 3.67 × 10⁴ L mol⁻¹ cm⁻¹), 312 (ε = 3.31 × 10⁴ L mol⁻¹ cm⁻¹) nm.

Crystal data. C₁₅H₁₈O₂, M = 228.28, orthorhombic, P 2₁ 2₁ 2₁ Z = 4, λ = 0.70930 Å, a = 8.000(2) Å, b = 11.2730(12) Å, c = 13.0490(19) Å, V = 1176.8(4) Å³, T = 293(2) K, Dc = 1.288 mg/m³, μ = 0.084 mm⁻¹, F(000) = 488, size = 0.40 × 0.35 × 0.22 mm³, reflections collected/unique = 1873/1873 [R(int) = 0.0000], final R indices [I > 2σ(I)]: R₁ = 0.0383, wR₂ = 0.0866, R indices (all data): R₁ = 0.0579, wR₂ = 0.0979. CCDC No. 245375.
1H), 2.02–1.84 (m, 3H), 1.84–1.72 (m, 1H), 1.71–1.63 (m, 2H), 2.62–2.49 (m, 2H), 2.38–2.22 (m, 1H), 2.15 (d, J = 2.85 (dd, J = 18 Hz, 7.6 Hz, 1H), 2.42–2.34 (m, 1H), 2.33–1.98 (m, 4H), 1.92–1.79 (m, 2H), 1.76–1.55 (m, 5H), 1.52–1.40 (m, 1H). 13C NMR (100 MHz, CDCl3): δ 223.15, 135.29, 128.21, 60.39, 58.36, 53.33, 51.26, 49.72, 45.87, 44.49, 40.10, 39.78, 29.96, 26.86. HRMS: 203.1438 (M+ + H) C14H16O2H requires 203.1436.

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References and notes
11. Andreotti, G. D.; Bohmer, V.; Jordan, G. J.; Tabayabai, M.; Ugozoli, F.; Vogt, W.; Wolff, A. J. Org. Chem. 1993, 58, 4023–4032. The compound 5 has been mentioned in this column of silica gel. The column was eluted with petroleum ether to remove the tin impurity. Further elution with petroleum ether–ethyl acetate (98:2) furnished the angular tetraquinane 12 (59 mg, 73%) as a colorless liquid. IR (film) νmax: 1737 cm−1. 1H NMR (400 MHz, CDCl3): δ 5.72–5.54 (m, 2H), 3.34–3.21 (br, m, 1H), 2.71–2.59 (complex m, 1H), 2.52–2.44 (dd, J = 18.6, 7.6 Hz, 1H), 2.42–2.34 (m, 1H), 2.33–1.98 (m, 4H), 1.92–1.79 (m, 2H), 1.76–1.55 (m, 5H), 1.52–1.40 (m, 1H). 13C NMR (100 MHz, CDCl3): δ 223.15, 135.29, 128.21, 60.39, 58.36, 53.33, 51.26, 49.72, 45.87, 44.49, 40.10, 39.78, 29.96, 26.86. HRMS: 203.1438 (M+ + H) C14H16O2H requires 203.1436.

References and notes
reference but the detailed procedure and data has not been reported.

