Synthesis of Two Bisanthrons via Their Corresponding Bislactone Intermediates and "Biscyclization" of Their Corresponding Dicarboxylic Acids

A.Shockravi and S. M. Khodaean: Teacher Training University

Abstract

Anthrons are important precursors for a variety of antitumor and antibiotic drugs. This work is towards the synthesis of two bisanthrons 6 and 10. These bisanthrons are synthesised via the corresponding bislactones 4 and 8 and the dicarboxylic acids 5 and 9 which respectively are formed through the cleavage of the above bislactones. We have taken advantage of the "biscyclization" method in the simultanious cyclization of the above dicarboxylic acids for the synthesis of corresponding bisanthrons.

Introduction

The "biscyclization" methodology have attracted attentions occasionally [1-5]. We have been able to synthesize the anthralin as an antipsoriatic drug via this methodology [6]. We also have reported the synthesis of some other biologically active potential compounds [7-10]. We have now used the same method for the preparation of bisanthrons. In this work we report the synthesis of another biologically potential active compounds via lactone and bislactone intermediates, taking advantage of the biscyclization process.

Anthrons are the reduction products of the anthraquinones. These compounds are used in dyes and drugs industries [11]. There are variety of methods for the generation of such cyclic compounds and their derivatives. These may be classified into three general categories: Diels - Alder reaction [12], nucleophilic and anionic condensation [13]. Friedel -Crafts alkylation (or acylation) [14].

We found that 3-aryl phthalides can be prepared in relatively good yields by the reactions of 3- bromophthalide 3 with an aromatic compound in the presence of SnCl₄ CH2Cl₂ solution at 0°C. Both 3 -aryl phthalides are converted to the corresponding bisanthrons. Another approach led us to the synthesis of the syn-pyromellitide (bislactone) 8 which afforded the diacid 9 via condensation with toluene. Simultanious cyclization of this diacid also led to bisanthron 10 under the same conditions.

Scheme l: i, NaBH4' DMF; ii. NBS, CCI4; iii. SnCI4' CH2CI~ P-dimethoxy benzene, iv. Zn, NaOH; v. H2S04 or PPA. vi. NaBH4; DMF; vii. AICI3' Toluene.

Conclusion

Our attempts led to the synthesis of the "bislactone" 4 intermediate which produced the diacid 5 through the cleavage of the corresponding lactone functional groups resulting to the bisanthron 6 which is a biologically potential active compound and

prepared through the bisacylation process (Scheme 1). This compound affords the "minimum structure" requirements in two sides for antipsoriatic activity [15]. This work demonstrates that through the simultanious cyclization method via bislactones intermediates we can prepare bisanthrons. We hope that using this method will lead to the synthesis of bisanthrons, which contain specific structural requirements of anticancer drugs. The advantage of this approach compared to the classical Friedel-Crafts method is shorter pathways in which five steps including protection and deprotection processes of carbonyl groups [10] are eliminated. Improvement of the yields needs further works in our laboratory.

Experimental

Melting points are uncorrected. NMR spectra were recorded at 60 MHz (lH)Hitachi 24RB and are reported in ppm downfield from TMS. Mass spectra were obtained by electron ioniztion, Variau incos 50. Infera red perkin Elmer 843.

Phthalide 2:

Reduction of the phthalic anhydride with NaBH₄. 2.0gr (0.05 mole) of NaBH₄ in 10 ml of DMF was stirred and cooled in an ice bath while 7.4 gr (0.05 mole) of phthalic anhydride in 40 ml of DMF was added in 15 min. The ice bath was removed and stirring was continued for 1 hr. 6N HCl (20 ml) was added with cautious and the mixture was concentrated. Water (100 ml) was added. The crude product was filtered and crystalized from petroleum ether (40-0 °C) and dried to give 4.84 g (72%) of phthalide 2. m.p. 68-70 °C (72 °C [16]).

 v max(film)1740s, 1600m, 1430m, 1280m, 1040s, 720s cm $^{-1}$. δ (60 MHz, CDCl₃)' 5.35(s,2H), 7.6(m,3H), 8.0(m, 1H).

Bromo phthalide 3:

Four grams (0.03 mole) of phthalide **2** and 5.4 gr (0.03 mole) N-bromosuccinimide (NBS), 0.2 gr benzoyl peroxide and 80 ml of dry redistilled carbon tetrachloride were

mixed in a 250 ml round-bottomed flask. The mixture was refluxed for 2 hours, by this time the mixture turned yellowish. The succinimide was filtered off and was washed with a little dry carbon terachloride. The solvent was removed by rotary evaporator, 6.1 g 3-bromo phthalide (96%) was obtained as colorless crytals which was recrystallised from cyclohexanone (m.p.77-78 °C). ^v_{max} (film)1800s, 1600w, 1430m, 1280m, 960s, 760s cm⁻¹. δ(60 MHz, CCl₄) 7.35(s,1H), 7.65(m,2H), 7,85(m, 1H), 8.2(m, 1H).

Bis- (1,3 -diphthalidyl) -2,5 -dimethoxybenzene, Bislactone 4

To a solution of 5.8 g(0.027 mole) of 3-bromo phthalide,1.8 g (0.0135 mole) 1,4-dimethoxy benzene and 40 ml CH ₂Cl ₂ in a dry 250 ml three necked round bottom flask equipped with a separatory funnel,condenser and trying tube 4.8 ml fuming SnCl₄ was added over 30 minutes at 0°C. Stirring was continued for six hours. The reaction mixture was added with stirring to a mixture of concentrated HCl (30 ml) and crushed ice (100 gr). The lower layer was separated and washed with water (250 ml) and dried with Na₂SO₄. Solvent was evaporated by rotary evaporator. A light brown oily material,6.7 g(61%) was obtained. TLC(ethyl acetate) showed one spot.

 $^{v}_{max}$ (film)1760s, 1600w, 1500m, 1280m, 1220m, cm⁻¹. δ (60 MHz, CCl₄) 3.75(s, 3H), 4.0(s, 3H), 6.25(s,2H), 6.8(m, 4H), 7.6(m,4H), 7.8-8.2(m,2H). m/z (El) 270 [100, (M-C₈H₅O₂).+], 138 [40.0, ((OMe)₂ C₆H₄).+], 133 [35.0, (C₈H₆O₂).+], 105 [65.0, (C₆H₄CH(OH).+].

1,3-(Bis-2-carboxybenzyl)-2,5- dimethoxybenzene 5

To a solution of 2 g(0.0049 mole) of the bis-(dipthalidyl)- 1,4- dimethoxybenzene 4 and 300 ml aqueous NaOH (10%) and 35 gr zinc was added and heated at reflux temperature for 48 hours. The hot mixture was filtrated and washed with hot water. The combined filtrates and washings were cooled and slowly added to ice (100 gr) containing HCl (10 ml) with stirring. The colorless precipitate was collected by filtration and recrystalized from ethanol and dried to give 0.38 g(19%) the bis acid 5 (m.p. 255-259 °C). v_{max} (film)3640-2800 strong and broad, 1750s, 1600w cm⁻¹. $\delta(60)$

MHz,acetone-d6) 3.3(s, 3H), 3.45(s, 3H), 4.35(s, 4H), 6.4-6.6(m,2H), 7.2-8(m,8H). m/z (El) 272 [100, (M.((COO) $C_6H_4CH_2)^{-+}$], 135 [5.0, ((COOH) $C_6H_4)^{-+}$], 105 [68.0, $(C_6H_5CO)^{-+}$], 91 [35.0, $(C_7H_7)^{-+}$].

5H,7H-Bisbenzo [b,i]- 9,10- dimethoxy -1,8- nthracendione; Bisanthron 6

In a 25 ml erlenmayer flask the bis acid **5** (0.1 gr) was added with stirring to concentrated sulphuric acid (5 ml). After four hours, the solution was poured on crushed ice (50 gr). The yellowish semi-solid material was obtained which we were not able to recrystallize it in a proper solvent. The yield was 33%. $^{\nu}_{max}$ (film)2950w, 1760s, 1600w, 1500s cm⁻¹. δ (60 MHz, CCl4) 3.75(s, 3H), 3.90(s, 3H), 6.6(s,4H), 7.4-8.0(m,8H). m/z (El) 372 [0.5, (M+2).+, C₂₄H₁₈O₄], 119 [12.0, (C₆H₄CH₂CO) +], 91 [8.0, (C₇H₇CO). +].

pyromellithide 8:

A mixture of 2.01 gr (0.05 mol) of NaBH₄ in 15 ml of DMF was strirred and cooled in an ice bath while 5.4 gr (0.025 mole) pyromellithic anhydride **7** in 60 ml of DMF was added in 30 min. The ice bath was removed and stirring was continued for 1h π . 6N HCl (20 ml) was added cautiously and the mixture was concentrated. Water (100 ml) was added and the precipitates were filtered and dried to give 3.8 gr (52%) (m.p. 255-257 °C). $^{\nu}_{\text{max}}$ (film)17508, 1630m, 1460m, 11608, 10608, 760m cm-1.0(60 MHz, CF₃COOD) 5.2(8, 4H), 7.8(8, 1H), 9.4(8, 1H).

1,5- (Bis-4-methylbenzyl)-2,4- dicarboxybenzene 9

5 gr (0.0263 mole) pyromelithide **8** was dissolved in 60 ml toluene in a 250 ml flask provided with a reflux condenser and protected by a calcium chloride tube; 20gr of anhydrous aluminum chloride was added and the mixture was heated for 8 hours. After cooling, 200 gr crushed ice and 100 ml concentrated HCl was added. The reaction mixture was extracted with 5% NaOH (2×50 ml). The combined aqueous NaOH poured into 15 ml concentrated HCl and 50 gr crushed ice. The preicipitate was filtered and

dried to give 1.95gr of a semi- solid meterial. The yield was 20%. v_{max} (film) 3600-2200 strong and broad, 1680 s, 1600m, 1280s; δ (60 MHz, acetone-d6) 2.3(s,6H), 4.3(s,4H), 7-7.3(m, 8H), 7.7-8.7(m,2H). m/z (El) 374 [1.0, (M.+) C₂₄H₂₂O₄)], 265 [100, (CH₃C₆H₄ CH₂C₆H₂ (CooH)2 (CH₂) -H₂O. +],283 [25, (CH₃C₆H₄ 105 [40.0, (CH₃C₆H₄CH₂).+], 91 [80.0, (CH₃C₆H₄).+].

5H, 7H, Bisluleo [b,i] -1,8-anthracenedione; Bisanthron 10

0.1 gr(0.00027mole)bisacid **9** was added slowly to a mixture of phosphorus pentoxide (10 gr) and phosphoric acid (4ml) and preheated at 100 °C for 0.5 hr with stirring. The heating was continued for 2 hr with occasional shaking. The mixture was cooled, decomposed with water (10 ml), and extracted with chloroform (2×25 ml). The solvent was washed with aqueous NaOH (50 ml) and then with water (50 ml) and dried with sodium sulfate. Removal of the solvent led to the product **10**. Low yield and NMR was not available.

 $v_{\text{max}}(\text{film})3010 \text{ s}, 2990 \text{ s}, 1780 \text{ s}, 1680 \text{ s}, 1620\text{s}, 1600\text{s}.\text{m/z}(\text{EI})337[0.5, (M-1).+, $$$$$$$$$C_{24}H_{18}O_2], 135 [5.0,((CH_2) C_6H_3CO).+],105[C_7H_5O.+],97[15(C_6H_9O).+],91 [8.0, (C_7H_7).+],69 [90.0, (C_5H_7).+].$

References

- 1. W.C. Christopfel and L.L. Miller; J.Org.Chem. (1984) 49, 5198.
- 2. W.L. Mosby; J.Org.Chem. (1954) 19,294.
- 3. F.C. Reitsch; C. Schmitz; J.M. Aubru; Tetrahedron lett. (1991)32, 3845.
- 4. T.R. Kelly; N.S. Chandsakumar and J.K. J. Saha Org. Chem. (1989) 54, 980.
- 5. T.R. Kelly; J.A. Field and Q. Li, Tetrahedron Lett. (1988) 29, 3545.
- 6. A. Shockravi and J.M.Bruce.; J.Sci. I.R. Iran; (1996) 7, 21.
- A. Shockravi and H. Jahanbin sardroudi,; Iran. J.Chem. and Chem. Eng. Vol. 18, No.1(1999)24.
- 8. A. Shockravi and J.M. Bruce; J.Sci. I.R. Iran. 10(1) (1999) 35.
- 9. A. Shockravi and K.A. Nasiri; Iran. J.Chem. and Chem. Eng. 16(1) (1997) 10.

- 10. A. Shockravi, J. M. Bruce; Iran. J.Chem. and Chem. Eng. 14(1) (1995) 23.
- 11. Donald W. Cameron and Andrew G. Riches, Tetrahedron Lett. 36 (13) (1995) 2331.
- 12. G.A. Krus; Li. Chen.; J.Org.Chem 56 (1991) 5098.
- 13. A. Gemot; J.E.L. Florent; Moneret. Tetrahedron. Lett. (1989) 30,711.
- 14. I.W. Smith; S.J. Ambler; D.J. Steggles. Tetrahedron. Lett. (1993) 34, 7447.
- 15. A. Krebs, H. Schaltegger and A. Scholtegger, Brit. J. Dermatol., 105, suppl. 20 (1981) 6.
- 16. D.M. Bailey, and E.W. Johnson, J.Org.Chem. (1970) 35, 3574.