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THE SYNTHESIS OF POLYCYCLIC STRUCTURES VIA TRICARBONYL CYCLOHEXADIENYL IRON COMPLEXES: SYNTHESIS OF 4b-METHYL-9-OXA AND 4b-METHYL-B-HOMO-9-KETO-9a-OXA-PERHYDROPHENANTHRENES (°)

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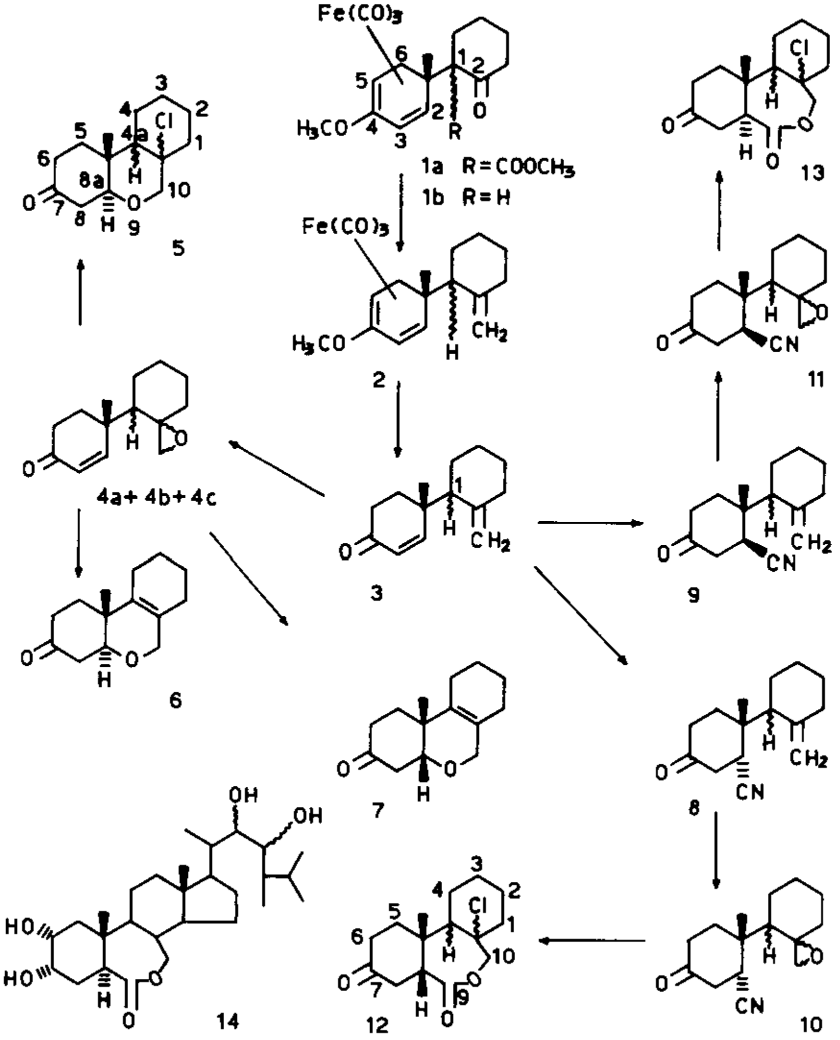
Abstract - A synthetic route to etherotricyclic structures by elaboration of tricarbonyl cyclohexadienyl iron complexes is described.

We are currently concerned in the synthetic elaboration of the iron cyclohexadienyl complexes as a new synthetic tool in the field of polycyclic natural compounds, especially terpenes and steroids.[1] We report now, by elaboration of the complex 1a previously obtained,[2] the synthesis of the model tricyclic oxa compound 5, 6, 7, as well as the lactones 12 and 13.
Complex 1a was decarboxylated[3] to give the ketone 1b that was converted, by the methodic of Takai et al.,[4] into the methylene derivative 2 (scheme). Compound 2, by decomplexation with trimethylamine-N-oxide then mild hydrolysis of corresponding enol ether with oxalic acid, afforded the enone 3.[5] This appears a useful intermediate to be converted into 6-oxa-tricyclic structures. At this purpose the enone 3 was epoxidized by m-chloroperbenzoic acid, to give three stereoisomeric epoxyenones.[6] By chromatographic separation the higher Rf isomer 4a was obtained as a pure compound, then the other isomers 4b + 4c as an inseparable mixture with the same Rf were eluted. By treatment of 4a with gaseous hydrochloric acid at room temperature the epoxy ring was opened to afford the corresponding primary alcohol that under the reaction conditions added to the enonic double bond, to give the tricyclic ether 5. Likewise, the epoxy enones mixture 4b + 4c under the same conditions afforded the tricyclic ethers 6 and 7. As to the stereochemistry of the carbon 8a located at the ring junction of the synthesized ethers 5, 6, and 7, this was deduced in the ^{1}H-NMR by the signal pattern of the H-8a proton.[7]
Moreover, the enone 3 was later converted into the model tricyclic lactones 12 and 13. By hydrocyanation of 3 with diethylaluminum cyanide two only nitriles 8 and 9 were obtained exhibiting the cyano group (NMR data) respectively in the axial and the equatorial position according to a stereoselective attack of diethylaluminum cyanide to each diastereoisomeric enone.[8] The next epoxydation reaction of compounds 8 and 9 gave the corresponding epoxynitriles 10 and 11, which in hydrolytic conditions (gaseous hydrochloric acid, dioxane) underwent the opening of the epoxy

ring as well as the hydrolysis at the cyano group to give the corresponding lactones 12 and 13. These reported synthetic elaborations of the complex 1a appear extensible, starting from suitable iron cyclohexadienyl complexes, to the synthesis of the biologically interesting 6-oxa- or 6-azasteroids[10] as well as of the compounds similar to the steroidic lactone brassinolide 14, a very active hormone regulator of the plant growth[11] exhibiting a lactonic structure very close to the synthesized lactone 13. With this purpose we prosecute further our research.

SCHEME



EXPERIMENTAL

IR Spectra were recorded with a Perkin-Elmer 257 Infracord; ^{1}H-NMR spectra with a Perkin-Elmer apparatus (90 MHz) in $CDCl_3$ using TMS as an internal standard; mass spectra of the reaction products were recorded with an AEI MS 12 apparatus. For TLC Kieselgel from Merck was used.

Tricarbonyl[1-(2-5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2-ketocyclohexane] iron (1b). Complex 1a (0.5 mM) was dissolved in 1.7 ml of HMPA and then tetramethylammonium acetate (80 mg) was added. The solution was warmed at 100°C with stirring under N_2 for 4 h, then water was added and the mixture extracted with ethyl ether; the ethereal extracts were washed with saturated sodium carbonate and water, then dried and evaporated. The crude mixture was chromatographed on silica gel. By eluting with hexane-ethyl ether (95:5) and then hexane-ether (90:10), 1b was obtained (65% yield) as a liquid compound. MS: m/z 360. ^{1}H-NMR ($CDCl_3$) δ : 5.0 (1H, mixed dd, C_3 olefinic proton), 3.6 (3H, s, OCH_3), 3.2 (1H, m, C_5 olefinic proton), 2.55-3.0 (2H, mixed signals, C_2 and C_6 protons), 1.0 (3H, s, angular methyl. IR ($CHCl_3$) ν_{max}: 2020, 1980, 1710 cm^{-1}. Anal. Calcd for $C_{17}H_{20}FeO_5$: C, 56.70%; H, 5.5%; Found: C, 56.1%; H, 5.1%.

Tricarbonyl[1-(2-5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2-methylenecyclohexane]iron (2). Powdered zinc (6.88 g) was added to a solution of methylene bromide in 70 ml of anhydrous THF under N_2. To this suspension 21 ml of a 1M solution of titanium tetrachloride in methylene chloride were added in a few minutes under stirring; at the end of the addition the resulting mixture was left to stir for additional 15 min. Then, a solution of 1b (1.05 g) in 6 ml of THF was added and the resulting mixture left to stir overnight. The resulting suspension was filtered and the solution washed before with acidic water, then until neutrality with water; the organic layer was dried and evaporated, and the resulting crude mixture was chromatographed on silica gel. By elution with hexane, 800 mg of 2 were obtained (80% yield). MS: m/z 358. ^{1}H-NMR ($CDCl_3$) δ : 5.0 (1H, mixed dd, C_3 proton), 4.75 and 4.55 (2H, mixed d, olefinic methylenic protons), 3.6 (3H, s, OCH_3), 3.25 (1H, m, C_5 proton), 2.65 - 2.0 (3H, mixed signals, C_2 and C_6 protons), 1.1 (3H, s, angular methyl IR ($CHCl_3$) ν_{max} : 2020, 1980, 1640 cm^{-1}. Anal. Calcd for $C_{18}H_{22}FeO_4$: C, 60.3%; H, 6.2; Found: C, 59.6; H, 5.9%.

1-(1-Methyl-4-keto-2-cyclohexenyl)-2-methylenecyclohexane (3). Compound 2 (1.5 g) was dissolved in 33.2 ml of anhydrous benzene under nitrogen, to which 4.1 g of trimethylamine N-oxide was then added under vigorous stirring at 85°C. After 4 h the reaction was stopped, water added and the resulting mixture extracted with diethyl ether. The ethereal extracts were washed many times with 2N HCl, then neutralized, dried and evaporated. The crude residue was chromatographed on silica gel. By eluting with petroleum ether (40-70°C) diethyl ether (90:10) 3 was obtained (650 mg) as a liquid compound. MS: m/z 204. ^{1}H-NMR ($CDCl_3$)δ : 1.22 (3H, s, angular methyl), 4.67 and 4.85 (2H, two broad s, olefinic methylenic protons), 5.82 and 5.85 (1H, mixed d, J_{2-3} 10Hz C_3 proton), 6.82 and 6.85 (1H, mixed dd, J_{2-3} 10Hz, J_{ha} 2Hz, C_2 proton). IR ($CHCl_3$) ν_{max} : 1650, 1670 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30%; H, 9.87%; Found: C, 82.45%, H, 9.66%.

1-(1-Methyl-4-keto-2-cyclohexenyl)-2-epoxymethylenecyclohexanes (4a), (4b), (4c). Compound 3 (490 mg) was dissolved in 5.74 ml of methylene chloride (distilled on calcium chloride). m-Chloroperbenzoic acid (810 mg) was added and this solution was left under stirring for 4 h. By thin layer examination the formation of two products at lower Rf was observed; a solution of sodium m-chlorobisulfite (1 g in 10 ml of water) was added to the reaction solution to destroy the peracid excess until a starch paper was colorless. Then this mixture was extracted with diethyl ether and the ethereal extracts were washed with 2N NaOH and water until neutral, then dried and evaporated. The crude residue was chromatographed on silica gel. By eluting with hexane-ethyl acetate (90:10) the higher Rf epoxide 4a was eluted (100 mg), microcrystals from hexane-diethyl ether, mp 74-77°C. MS: m/z 220. ^{1}H-NMR δ: 1.25 (3H, s, angular methyl), 2.5 and 3.10 (2H, two d, epoxidic protons J_{gem} 4Hz), 5.82 (1H, d, C_3 olefinic proton J_{2-3} 10Hz), 6.87 (1H, dd, C_2 olefinic proton J_{ha} 2Hz). IR ($CHCl_3$) ν_{max}: 1670 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32%, H, 9.15%. Found: C, 75.94%; H, 9.43%. By further elution an inseparable mixture of 4b + 4c (150 mg), exhibiting the same Rf, was obtained. ^{1}H-NMR δ: 1.23 and 1.25 (3H, mixed two s, angular methyl), 2.30-2.90 (2H, mixed d, epoxydic protons), 5.77 and 5.85 (1H, mixed d, C_3 olefinic proton J_{2-3} 10Hz), 6.80 and 6.95 (1H, mixed dd, C_2 olefinic proton J_{hal} 2Hz). IR ($CHCl_3$) ν_{max}: 1670 cm^{-1}.

4b-Methyl-7-keto-9-oxa-10a-chloroperhydrophenanthrene (5). Compound 4a (200 mg) was dissolved in 9 ml of anhydrous dioxane and the resulting solution, saturated with gaseous HCl, was left overnight under stirring at room temperature. After total evaporation of the solvent, the residue was extracted with methylene chloride, then the extracts were washed until neutral and evaporated; 150 mg of a crude product was obtained. By chromatography on silica gel eluting with hexane-diethyl ether (90:10) the ether 5 (100 mg) was obtained as prisms from hexane-diethyl ether, mp 134-137°C. MS: m/z 256. ^{1}H-NMR δ: 1.22 (3H, s, angular methyl), 3.60 (1H, m, C_{8a} proton $W_{1/2}$ 10Hz), 3.87 (2H, dd, C_{10}, J_{gem} 12Hz), IR ($CHCl_3$) ν_{max}: 1710 cm^{-1}; then a mixture of byproducts (30 mg) was further eluted. Anal. Calcd for $C_{14}H_{21}O_2Cl$: C, 65.48%, H, 8.24%. Found: C, 65.69%; H, 8.47%.

4b-Methyl-7-keto-9-oxa-$\Delta^{4a(10a)}$-perhydrophenanthrenes (6) and (7). The compounds 4b + 4c (200 mg) by reaction with gaseous HCl in the conditions previously reported gave, by thin layer examination, a mixture of two main compounds. After the usual work up, a crude mixture (130 mg) was obtained, which, by chromatography on silica gel eluting with hexane-diethyl ether (90:10), gave 6 (40 mg) as a liquid compound. MS: m/z 220. ^{1}H-NMR δ: 1.12 (3H, s, angular methyl), 3.63 (1H, m, C_{8a} proton $W_{1/2}$ 10Hz), 3.9 (2H, br. s, C_{10} protons). IR ($CHCl_3$) ν_{max}: 1710 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32%; H, 9.15%. Found: C, 76.67%; H, 9.51%. By further elution 7 (70 mg) was obtained; prisms from hexane-diethyl ether, mp 130-132°C. MS: m/z 220. ^{1}H-NMR δ: 1.1 (3H, s, angular methyl), 3.82 (2H, s, C_{10} protons), 4.03 (1H, t, C_{8a} proton J 7Hz). IR ($CHCl_3$) ν_{max}: 1710 cm^{-1}; finally a minor compound (15 mg) eluted was not investigated any further. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32%, H, 9.15%. Found: C, 76.03%; H, 8.97%.

1-(1-Methyl-4-keto-2-cyanocyclohexyl)-2-methylenecyclohexanes (8) and (9). Compound 3 (564 mg) was dissolved in 6.66 ml of anhydrous THF under nitrogen and stirring at 0°C, then 4.54 ml of a 2.4 N solution of Et_2AlCN in toluene was added. The stirring was continued overnight whereas the temperature was left to rise to room temperature. The reaction mixture was poured into 2N NaOH and the resulting mixture was extracted with diethyl ether, the ethereal extracts were washed until neutral, dried and evaporated. By thin layer examination the formation of two compounds was noted. By chromatography on silica gel, eluting with benzene-diethyl ether (98:2), the higher Rf cyano derivative 8 was isolated (230 mg) as a liquid compound. MS: m/z 231. ^{1}H-NMR δ: 1.32 (1H, s, angular methyl), 3.30 (1H, t, C_2 proton J 10Hz), 4.80 (2H, m, olefinic protons). IR ($CHCl_3$) ν_{max}: 1640, 1715, 2240 cm^{-1}. Anal. Calcd for $C_{15}H_{21}ON$: C, 77.88%; H, 9.15%. Found: C, 77.47%; H, 9.05%. Afterwards, the lower Rf isomer 9 (260 mg) was eluted as a liquid compound. MS: m/z 231. ^{1}H-NMR δ: 1.25 (3H, s, *angular methyl*), 3.28 (1H, m, C_2 proton $W_{1/2}$ 12Hz). IR ($CHCl_3$) ν_{max}: 1640, 1715, 2240 cm^{-1}. Anal. Calcd for $C_{15}H_{21}ON$: C, 77.88%; H, 9.15%. Found: C, 77.49%; H, 9.31%.

1-(1-Methyl-4-keto-2-cyanocyclohexyl)-2-epoxymethylenecyclohexanes (10) and (11). Cyano compound 8 was dissolved in 2.9 ml of methylene chloride. m-Chloroperbenzoic acid (313 mg) was added at 0°C under stirring; the reaction was left to proceed overnight. After the usual work up, by thin layer examination, the formation of the main liquid compound 10 (180 mg) was observed. MS: m/z 247. ^{1}H-NMR δ : 1.3 (3H, s, angular methyl), 2.55 and 3.5 (2H, two d, J 8Hz, epoxydic protons), 3.0 (1H, m, C_2 proton). IR ($CHCl_3$) ν_{max}: 1720, 2230 cm^{-1}. Anal. Calcd for $C_{15}H_{21}O_2N$: C, 72.84%; H, 8.56%. Found: C, 72.49%; H, 8.45%. In the same conditions the stereoisomer 9 gave the epoxyde 11 as a liquid compound. MS: m/z 247. ^{1}H-NMR : 0.95 (3H, s, angular methyl), 2.0-2.6 (2H, m, superimposed epoxydic protons), 3.0 (1H, m, C_2 proton). IR ($CHCl_3$) ν_{max}: 1720, 2230 cm^{-1}. Anal. Calcd for $C_{15}H_{21}O_2N$: C, 72.84%; H, 8.56. Found: C, 72.51%; H, 8.61%.

4b-Methyl-7,9-diketo-B-homo-9a-oxa-10a-chloroperhydrophenanthrenes (12) and (13). Compound 10 (300 mg) was dissolved in 23 ml of anhydrous dioxane, then the resulting solution was saturated with gaseous HCl and left overnight under stirring at room temperature. After evaporation to dryness, the residue was extracted with methylene chloride and the organic extracts washed until neutral, dried and evaporated. By chromatography of the residue on grade IV acidic alumina eluting with benzene, a mixture of compounds (150 mg) was eluted, then the lactone 12 (80 mg) as a solid at low melting point was obtained. MS: m/z 284. ^{1}H-NMR δ: 1.20 (3H, s, angular methyl), 3.75 (1H, m, C_{8a} proton), 4.0 (2H, s, C_{10} protons). IR ($CHCl_3$) ν_{max}: 1730 cm^{-1}. Anal. Calcd for $C_{15}H_{21}O_3Cl$: C, 63.26%; H, 7.43%. Found: C, 63.52%; H, 7.60%. The above eluted mixture (150 mg) was submitted to strong hydrolytic conditions (2 ml of dioxane, 2 ml of conc. HCl, 100°C overnight) to give more lactone 12 (80 mg). Likewise, cyanoepoxy compound 11 gave the lactone 13, microcrystals from methylene chloride diethyl ether, mp 137-141°C. MS: m/z 284. ^{1}H-NMR δ: 1.13 (3H, s, angular methyl), 3.72 (1H, m, C_{8a} proton), 4.0 (2H, s, C_{10} protons). IR ($CHCl_3$) ν_{max}: 1725, 1735 cm^{-1}. Anal. Calcd for $C_{15}H_{21}O_3Cl$: C, 63.26%; H, 7.43%. Found: C, 63.01%; H, 7.21%.

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REFERENCES AND NOTES

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5. Obtained as an inseparable diastereoisomeric mixture at C_1. The reported structures are supplied by their ^{1}H-NMR, IR, and Mass spectra, which are summarized in the Experimental.
6. A fourth epoxy-enone isolated in a very low yield was not investigated further.
7. H-8a appears in 6 as a complex multiplet as well as a triplet in the epimer 7 according to, by Dreiding models examination, an α and a β orientation, respectively. The α orientation was also assigned to H-8a proton of 5 very similar (signal pattern, chemical shift) to the corresponding proton of 6. More work is needed to define the stereochemistry of the other carbons 4a and 10a in the compound 5.
8. By the strong shielding effect of deuterobenzene on the angular methyl of enone 3[9] we concluded that this methyl should be axially oriented.
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