

REACTIONS OF IRON PENTACARBONYL WITH SOME STEROID DIENES

HOWARD ALPER AND JOHN T. EDWARD

Department of Chemistry, McGill University, Montreal, Canada

(Received May 16th, 1968)

SUMMARY

Tricarbonyliron complexes of steroidal $\Delta^{2,4}$ - and $\Delta^{5,7}$ -dienes have been prepared. The transoid $\Delta^{3,5}$ - and $\Delta^{4,6}$ -dienes, when heated with iron pentacarbonyl, rearrange to form the cisoid $\Delta^{2,4}$ -diene complexes. Complex formation, followed by liberation of the diene ligand, thus offers a means of converting heteroannular steroidal dienes into their thermodynamically less stable homoannular isomers.

A variety of simple dienes displace carbon monoxide from iron pentacarbonyl to give dieneiron tricarbonyl complexes¹⁻³. However, the only steroidal diene reported to have reacted in this way is ergosterol acetate; attempts to carry out the reaction with ergosterol failed⁴. We have now found that ergosterol [V; R=OH, R'=CH(CH₃)-CH=CH-CH(CH₃)-CH(CH₃)₂] and the other steroidal dienes listed in

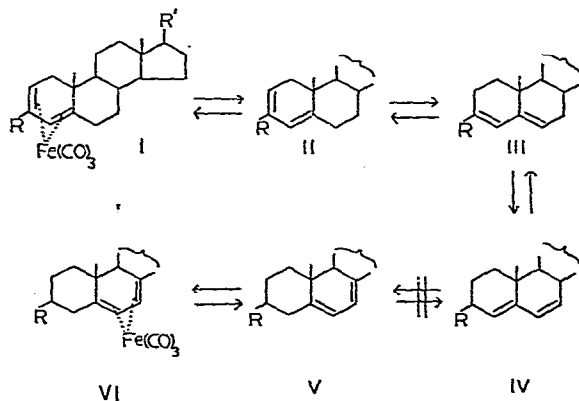


Table 1 react with iron pentacarbonyl under suitable conditions to give tricarbonyliron complexes in 30–70% yield. Most of the complexes were moderately stable when stored in a refrigerator but slowly decomposed at room temperature; however, the complex of ergosterol had to be chromatographed and stored under nitrogen.

The complexes exhibited the expected infrared (Table 2) (*cf.* ref. 5) and nuclear magnetic resonance spectra (Table 3) (*cf.* refs. 6, 7). The conversion of the dienes (II or V) into their iron tricarbonyl complexes (I or VI) results in a large hypsochromic shift and an increase in intensity of their ultraviolet absorption peaks (Table 4). These

TABLE 1

REACTIONS OF DIENES WITH IRON PENTACARBONYL

Diene ^a	Solvent	Time (h)	Complex structure ^a	Yield (%)
II; R=H	Isooctane	40	I; R=H	63
III; R=H	Dibutyl ether	36	I; R=H	64
IV; R=H	Dibutyl ether	108	I; R=H	34
III; R=CH ₃	Dibutyl ether	36	I; R=CH ₃	53
III; R=OCH ₃	Dibutyl ether	36	I; R=OCH ₃	71
V; R=OH	Dibutyl ether	14	VI; R=OH	42
V; R=OH ^b	Isooctane	30	VI; R=OH ^b	39

^a R' = C₈H₁₇ except. ^b R' = CH(CH₃)-CH=CH-CH(CH₃)-CH(CH₃)₂.

TABLE 2

CARBONYL STRETCHING BANDS OF IRON TRICARBONYL COMPLEXES

Complex ^a	Phase	Bands ^c (cm ⁻¹)
I; R=H	Neat	2036s, 1964s, 1938s, 1925sh, 1916sh
I; R=CH ₃	CCl ₄	2040s, 1970s
I; R=OCH ₃	KBr	2038s, 1966s
VI; R=OH	KBr	2029s, 1957s
VI; R=OH	CHCl ₃	2031s, 1960s
VI; R=OH ^b	KBr	2032s, 1958s, 1928w
VI; R=OH ^b	CHCl ₃	2034s, 1962s, 1928w

^a R' = C₈H₁₇ except. ^b R' = CH(CH₃)-CH=CH-CH(CH₃)-CH(CH₃)₂. ^c s=strong, w=weak, sh=shoulder.

TABLE 3

CHEMICAL SHIFT (δ) IN NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PROTONS ON CENTRAL CARBON ATOMS OF DIENE SYSTEM

Compound	Solvent	δ (ppm)
II; R=H, R'=C ₈ H ₁₇	CDCl ₃	5.41, 5.75
I; R=H, R'=C ₈ H ₁₇	CCl ₄	5.14, 5.62
V; R=OH, R'=C ₈ H ₁₇	CDCl ₃	5.43, 5.63 (<i>J</i> =5.5 cps)
VI; R=OH, R'=C ₈ H ₁₇	CDCl ₃	4.98, 5.25 (<i>J</i> =5.0 cps)
V; R=OH, R'=C ₉ H ₁₇	CDCl ₃	5.26, 5.53 (<i>J</i> =7.0 cps)
VI; R=OH, R'=C ₉ H ₁₇	CDCl ₃	5.24 ^a

^a Center of unresolved multiplet.

peaks probably result from $\pi \rightarrow \pi^*$ electronic transitions⁸. Cais and Maoz⁸ observed a peak at 229 μ in the spectrum of di-1-cyclohexenyliron tricarbonyl, a wavelength close to those of the complexes listed in Table 4. The direction of the shift of the ultra-violet absorption maximum is in accordance with the NMR results in indicating less olefinic character in the diene on complexation.

The structures for the complexes I and VI were confirmed by treating them

with ferric chloride according to standard procedures⁹ and recovering the cisoid dienes II and V. The formation of the complex I from the transoid dienes III or IV must consequently require the isomerization of the latter to the cisoid diene II. Shifts of double bonds under the influence of iron pentacarbonyl are well known²; however, the isomerization III or IV $\rightarrow$ II would be expected to be thermodynamically

TABLE 4

ULTRAVIOLET ABSORPTION PEAKS OF DIENES AND DIENEIRON TRICARBONYL COMPLEXES

Compound ^a	Solvent	λ_{max} (m μ)	log ϵ_{max}
II; R=H	Diethyl ether	267, 275	3.8 ¹⁷
I; R=H	Isooctane	231	4.24
I; R=CH ₃	Isooctane	233	4.28
II; R=OCH ₃	Ethanol	277	4.08
I; R=OCH ₃	Ethanol	237	4.37
V; R=OH	Hexane	281	4.04
VI; R=OH	Isooctane	238	4.34
V; R=OH ^b	Isooctane	281	4.00
VI; R=OH ^b	Isooctane	238	4.33

^a R' = C₈H₁₇ except. ^b R' = CH(CH₃)-CH=CH-CHCH₃-CH(CH₃)₂.

unfavourable (*cf.* ref. 10), and the overall change III or IV $\rightarrow$ I is possible because of a sufficiently favourable free energy change for the last step (II $\rightarrow$ I). The formation of these complexes, followed by their decomposition with ferric chloride, thus offers a means of converting transoid dienes into their less stable cisoid isomers. We have, in this way, prepared the hitherto unknown 3-methoxycholesta-2,4-diene (II; R = OCH₃, R' = C₈H₁₇) from 3-methoxycholesta-3,5-diene (III; R = OCH₃, R' = C₈H₁₇). The homoannular structure II (R = OCH₃, R' = C₈H₁₇) of the new compound follows from its UV spectrum (Table 4) (*cf.* ref. 11). The formation of the complex I (R = H, R' = C₈H₁₇) from IV (R = H, R' = C₈H₁₇) is very slow*, as would be expected from the extensive isomerization required. The failure to form VI (R = H, R' = C₈H₁₇) is at first sight surprising, since the isomerization required is less extensive. It is probable that dienes of structure V are considerably more strained than those of structure II (*cf.* ref. 12) and hence the energy barrier for the change IV $\rightarrow$ V would be substantially greater than the energy barriers for the change IV $\rightarrow$ III $\rightarrow$ II.

EXPERIMENTAL

General

Melting points were measured in capillary tubes in a Gallenkamp apparatus and are corrected. Microanalysis were performed by: Dr. C. Daesslé, Montreal; Bernhardt Mikroanalytisches Laboratorium, Mulheim, Germany; and Schwarzkopf Microanalytical Laboratory, Woodside, New York. Infrared spectra were obtained on Perkin-Elmer 137, 337 or 521 Spectrophotometers; the wavelength readings were

* When the reaction time was reduced to 40 hours, the yield of complex dropped to 4%. The yield shown in Table I for this and other reactions is not necessarily the maximum; no systematic study of optimum reaction conditions was made.

calibrated with a polystyrene film. Ultraviolet spectra were recorded on a Unicam SP-800 or Perkin-Elmer 350 spectrophotometer. Nuclear magnetic resonance spectra of carbon tetrachloride or deuteriochloroform solutions were obtained with a Varian A-60 Spectrometer.

Iron pentacarbonyl (Alfa Inorganics, Inc.) was used as received; distillation of the compound did not improve results. Solvents were dried and purified by standard methods. Ergosterol and cholesta-5,7-dien-3 β -ol were commercial products; cholesta-3,5-diene¹³, 3-methylcholesta-3,5-diene¹⁴ and 3-methoxycholesta-3,5-diene¹⁵ were prepared according to the literature; and cholesta-4,6-diene was kindly donated by Dr. M. M. Frojmovic. Melting points of the dienes agreed with values reported in the literature.

Cholesta-2,4-diene (II, R = H, R' = C₈H₁₇)

The following procedure is an improvement of that of Staveley and Bergmann¹⁶, who obtained the diene in 10–15% yield. A mixture of cholesterol (75 g) and chromatographic alumina (50 g) was heated for 2 h to 200–225° under 0.2 mm pressure. The cooled mixture was extracted with ether, and the oily material thus obtained was chromatographed on neutral alumina. Elution with benzene gave cholesta-2,4-diene in 55% yield, m.p. 64–66° (lit.¹⁷ m.p. 68.5°).

Preparation of iron tricarbonyl complexes

A mixture of the diene (2–15 mmoles) and iron pentacarbonyl (6–42 mmoles) in dry isooctane, cyclohexane or butyl ether (40–200 ml) was refluxed while stirred under nitrogen. Reaction conditions are given in Table 1. The mixture was cooled and filtered, and the filtrate evaporated at *ca.* 30 mm to remove solvent and unreacted iron pentacarbonyl. The residues were purified in different ways. Reasonably pure cholesta-2,4-dieneiron tricarbonyl (I; R = H, R' = C₈H₁₇) and its 3-methyl derivative (I; R = CH₃, R' = C₈H₁₇) could be obtained by dissolving the residue in acetone, filtering, and concentrating the filtrate. Further purification was effected by chromatography on Florisil using benzene as an eluant. 3-Methoxycholesta-2,4-dieneiron tricarbonyl (I; R = OCH₃, R' = C₈H₁₇) in benzene, and cholesta-5,7-diene-3 β -oliron tricarbonyl (VI; R = OH, R' = C₈H₁₇) in hexane, were chromatographed on Florisil. Crude ergosteroliron tricarbonyl (VI; R = OH, R' = C₉H₁₇) was chromatographed on neutral alumina under nitrogen. Elution with methylene chloride/ether (1/1) gave a brownish-green solid, which was rechromatographed on alumina with chloroform

TABLE 5

PROPERTIES OF DIENEIRON TRICARBONYL COMPLEXES

Complex	M.p. (°C)	Empirical formula	Calcd. (%)		Found (%)	
			C	H	C	H
I; R = H, R' = C ₈ H ₁₇	18–20	C ₃₀ H ₄₄ FeO ₃	70.86	8.72	70.84	8.93
I; R = CH ₃ , R' = C ₈ H ₁₇	18–20	C ₃₁ H ₄₆ FeO ₃	71.25	8.89	71.07	8.88
I; R = OCH ₃ , R' = C ₈ H ₁₇	24–27	C ₃₁ H ₄₆ FeO ₄	69.14	8.61	69.35	8.44
VI; R = OH, R' = C ₈ H ₁₇	49–51	C ₃₀ H ₄₄ FeO ₄	68.68	8.46	68.58	8.71
VI; R = OH, R' = C ₉ H ₁₇	70–71	C ₃₁ H ₄₄ FeO ₄	69.39	8.27	69.19	7.91

as eluant. The solid thus obtained was dissolved in dry acetone, and the solution filtered and concentrated to give yellow-brown crystals of ergosteroliron tricarbonyl. The complex decomposed in air, and hence was kept under nitrogen.

The other complexes were yellow or yellow-orange crystalline substances. Their melting points and analyses are given in Table 5.

Regeneration of dienes from diene complexes

The dieneiron tricarbonyl complex (2.0–2.6 mmole) in ethanol (10–15 ml) was added dropwise to a stirred solution of ferric chloride (*cf.* ref. 9) in 95% ethanol (8–10 ml). The mixture was stirred for 2 h at room temperature, poured into excess water and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and concentrated to yield fairly pure diene, identified by melting point and mixed melting point. Yields and melting points were: cholesta-2,4-diene, 90%, m.p. 65.0–67.0° (lit.¹⁷ m.p. 68.5°); 3-methylcholesta-2,4-diene, 75%, m.p. 67.0–69.0° (lit.¹⁴ m.p. 68–69°); cholesta-5,7-dien-3 β -ol, 84%, m.p. 148.0–150.0° (lit.¹⁸ m.p. 150–151°); ergosterol, 87%, m.p. 162.0–163.0° (lit.¹⁸ m.p. 162–164°); 3-methoxycholesta-2,4-diene, 59%, m.p. 55.0–56.0° (Found: C, 84.01; H, 11.54. C₂₈H₄₆O calcd.: C, 84.35; H, 11.63%).

ACKNOWLEDGEMENT

We are grateful to the National Research Council of Canada for financial support and for the award of a studentship (to H.A., 1965–66 and 1966–67).

REFERENCES

- 1 R. PETTIT AND G. F. EMERSON, *Adv. Organometal. Chem.*, 1 (1964) 1.
- 2 R. PETTIT, G. F. EMERSON AND J. MAHLER, *J. Chem. Educ.*, 40 (1963) 175.
- 3 P. L. PAUSON, *Organometallic Chemistry*, Arnold, London, 1967, pp. 120–126.
- 4 A. NAKAMURA AND M. TSUTSUI, *J. Med. Chem.*, 6 (1963) 796.
- 5 (a) K. NAKAMOTO, *Infrared Spectra of Inorganic and Coordination Compounds*, Wiley, New York, 1963, pp. 177–179;
(b) B. F. HALLAM AND P. L. PAUSON, *J. Chem. Soc.*, (1958) 646.
- 6 M. L. H. GREEN, L. PRATT AND G. WILKINSON, *J. Chem. Soc.*, (1959) 3753.
- 7 H. S. GUTOWSKY AND J. JONAS, *Inorg. Chem.*, 4 (1965) 420.
- 8 M. CAIS AND N. MAOZ, *J. Organometal. Chem.*, 5 (1966) 370.
- 9 G. F. EMERSON AND R. PETTIT, *J. Org. Chem.*, 29 (1964) 3620.
- 10 L. F. FIESER AND M. FIESER, *Steroids*, Reinhold, New York, 1959, p. 264.
- 11 A. I. SCOTT, *Interpretation of the Ultraviolet Spectra of Natural Products*, Macmillan, New York, 1964, pp. 47–49.
- 12 P. BLADON, J. M. FABIAN, H. B. HENBEST, H. P. KOCH AND G. W. WOOD, *J. Chem. Soc.*, (1951) 2402; H. B. HENBEST, G. D. MEAKINS AND G. W. WOOD, *J. Chem. Soc.*, (1954) 800; H. B. HENBEST, G. D. MEAKINS, B. NICHOLLS AND R. A. L. WILSON, *J. Chem. Soc.*, (1957) 997.
- 13 F. C. CHANG AND N. F. WOODS, *Steroids*, 4 (1964) 55; E. S. WALLIS, E. FERNHOLZ AND F. T. GEPHART, *J. Amer. Chem. Soc.*, 59 (1937) 137.
- 14 N. F. KUCHEROVA AND M. I. USHAKOV, *Zh. Obshch. Khim.*, 23 (1954) 315; *Chem. Abstr.*, 48 (1954) 2744g.
- 15 G. JUST AND C. C. LEZNOFF, *Can. J. Chem.*, 42 (1964) 79.
- 16 H. G. STAVELEY AND W. BERGMANN, *J. Org. Chem.*, 1 (1936) 575.
- 17 E. L. SKAU AND W. BERGMANN, *J. Org. Chem.*, 3 (1938) 166.
- 18 C. D. HODGMAN, *Handbook of Chemistry and Physics*, Chemical Rubber Publishing Co., Cleveland, 46th edn., 1966.