Ag(I) COMPLEXES OF $F_{2\alpha}$ PROSTAGLANDINS

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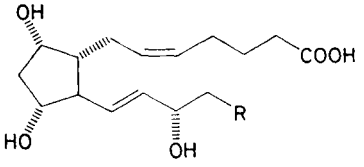
$PGF_{2\alpha}$ *I* and its synthetic analogs Cloprostenol *II* and Fluprostenol *III* form crystalline complexes with $AgNO_3$. Application of these compounds to the production of pure prostaglandins is described. ^1H and ^{13}C NMR spectra are also discussed.

Numerous syntheses of prostaglanding $F_{2\alpha}$ and its analogs have been described in literature[1-4]. The chromatographic separation of isomeric prostaglandins on $AgNO_3$-doped silica gel was repeatedly published[5-9]. We have recently observed the formation of a crystalline substance when using the mentioned type of chromatography.

Our present contribution deals with a practical method of preparation of complexes *IV–VI*, their NMR spectra as well as the use of these compounds in production of pure prostaglandins *I–III*.



(+) *I*, R = *n* - C_4H_9
(±) *II*, R = *m* - chlorophenoxy
(±) *III*, R = *m* - trifluoromethylphenoxy

The complexes *IV–VI* crystallize from an equimolar solution of both components in a suitable mixture of solvents. The complexes are decomposed by means of a sodium chloride solution.

As far as the structure of complexes *IV–VI* is concerned, we assume that the substantial interaction is that between the silver ion and the carbon atoms of both

prostaglandin double bonds. This is in accordance with chemical shifts changes observed in ^1H and ^{13}C NMR spectra of the relevant compounds. All NMR data are summarized in Table I (^1H NMR shifts for compounds *II*–*VI*), Table II (^1H NMR coupling constants for compounds *II*–*VI*), Table III (^{13}C NMR chemical shifts found for compounds *I*–*VI*).

^1H NMR spectra of *II*, *III*, *V*, *VI* and ^{13}C NMR spectra of *I*–*VI* were studied in detail. In the ^1H NMR spectrum of compound *II*, four multiplets are observed in the aromatic protons area, which corresponds to the *m*-chlorophenoxy group, followed by the peaks of the four protons on double bonds, those of the five CH—O protons, and finally those of the remaining twelve $CH(CH_2)$ protons in the molecule. The olefinic peaks at $\delta = 5{\cdot}48$ and $5{\cdot}67$ belong to the double bond in configuration *Z*, position C-5, C-6. The multiplet at $\delta = 5{\cdot}84$ with an intensity of two protons corresponds then to the second double bond, position C-13, C-14. On the basis of a detailed analysis of the ^1H NMR spectrum, peaks in the spectrum were assigned to all protons in the molecule. With the exception of protons H-7 (H-8) and the

TABLE I

^1H NMR chemical shifts for compounds *II*–*VI* in tetradeuteriomethanol

Proton	*II*	*V*	Δδ	*III*	*VI*	Δδ
H-2	2·42 bt	2·45 bt	+0·03	2·40 t	2·45 t	+0·05
H-3	1·78 m	1·84 m	+0·06	1·77 m	1·82 m	+0·05
H-4	2·24 bq	2·32 bq	+0·08	2·23 bq	2·31 bq	+0·08
H-5	5·48 m	5·75 dtt	+0·27	5·47 m	5·70 m	+0·23
H-6	5·67 m	5·92 dtt	+0·25	5·67 m	5·88 m	+0·21
H-7	~2·30	~2·43	—	2·35 bt	2·42 bt	+0·07
H-8	~2·30	~2·43	—	2·47 dq	2·48 dq	+0·01
H-9	4·03 dt	4·03 dt	0·00	4·03 ddd	4·03 ddd	0·00
H-10	1·77 ddd	1·78 ddd	+0·01	1·77 ddd	1·78 ddd	+0·01
H-10′	2·52 ddd	2·60 ddd	+0·08	2·53 ddd	2·59 ddd	+0·06
H-11	4·26 dt	4·33 bdt	+0·07	4·26 dt	4·32 bdt	+0·06
H-12	1·65 ddd	1·84 m	+0·19	1·65 ddd	1·86 m	+0·21
H-13	5·84	6·02	+0·18	5·86	6·00	+0·14
H-14	5·84	6·02	+0·18	5·86	6·00	+0·14
H-15	4·60 m	4·66 m	+0·06	4·64 m	4·69 m	+0·05
H-16	4·08 dd	4·11 dd	+0·03	4·14 dd	4·17 dd	+0·03
H-16′	4·14 dd	4·19 dd	+0·05	4·21 dd	4·25 dd	+0·04
H-18	7·13 dt	7·14 bt	+0·01	7·32–7·41	7·34–7·42	—
H-20	7·08 ddd	7·09 ddd	+0·01	7·32–7·41	7·34–7·42	—
H-21	7·39 dt	7·40 t	+0·01	7·62 m	7·62 m	0·00
H-22	7·04 ddd	7·05 ddd	+0·01	7·32–7·41	7·34–7·42	—

above-mentioned protons H-13 (H-14), values of chemical shifts and coupling constants were obtained for all peaks found in the spectrum. The relevant data for compounds *II*, *III*, *V*, and *VI* are given in Tables II and III. It follows from the observed differencies in chemical shifts that the preferred interaction between the silver atom and the molecule *I*, or *II* occurs in the area of the double bonds, without any of the two double bonds being preferred in a significant manner. We attempted to confirm the above described findings *via* analyses of ^{13}C NMR spectra. For the assignment of the indiviual peaks, the ^{13}C NMR spectrum of *I* as published by Cooper[10] was employed. However, peaks of double bonded atoms C-5, C-6, C-13, and C-14 (all being CH carbons) in compounds *II*, *III*, *V*, *VI* are found in the aro-

TABLE II

Coupling constants J_{HH} for compounds *II*, *III*, *V*, *VI* in tetradeuteriomethanol

Coupling constant	*II*	*V*	*III*	*VI*
J(H-2, H-3)	7·0	7·2	7·3	7·3
J(H-3, H-4)	7·0	7·2	7·3	7·3
J(H-4, H-5)	7·0	7·2	7·3	7·3
J(H-5, H-6)	10·8	10·5	10·8	10·6
J(H-5, H-7)	1·4	1·2	1·4	1·2
J(H-6, H-7)	7·0	7·0	7·3	7·2
J(H-6, H-4)	1·3	1·0	1·5	1·0
J(H-7, H-8)	[a]	[a]	7·3	7·3
J(H-8, H-9)	7·4	7·8	7·3	7·8
J(H-8, H-12)	11·0	*a*	11·2	11·2
J(H-9, H-10)	5·4	5·9	5·4	5·8
J(H-9, H-10′)	8·2	8·2	8·3	8·4
J(H-10, H-11)	2·3	2·4	2·4	2·5
J(H-10′, H-11)	5·4	5·3	5·4	5·6
J(H-11, H-12)	5·4	5·3	5·4	5·6
J(H-12, H-13)	9·0	*a*	9·0	*a*
J(H-15, H-16)	6·4	6·3	6·5	6·6
J(H-15, H-16′)	4·6	4·6	4·5	4·4
J(H-16, H-16′)	9·6	9·8	9·6	9·6
J(H-18, H-20)	2·0	2·0	*a*	*a*
J(H-18, H-21)	0·6	*a*	*a*	*a*
J(H-18, H-22)	2·2	2·2	*a*	*a*
J(H-20, H-21)	7·8	8·0	8·2	8·2
J(H-20, H-22)	1·0	1·0	*a*	*a*
J(H-21, H-22)	8·3	8·3	8·3	8·3

[a] Not determined.

TABLE III

^{13}C NMR chemical shifts for compounds *I*—*VI* in tetradeuteriomethanol

Carbon	*I*[a]	*I*[b]	*IV*[b]	Δδ	*II*	*V*	Δδ	*III*	*VI*	Δδ
1	174·3 s	174·5 s	[c]	—	177·2 s	177·2 s	0·0	177·4 s	177·3 s	−0·1
2	33·5 t	33·4 t	33·5 t	+0·1	34·4 t	34·2 t	−0·2	34·3 t	34·3 t	0·0
3	24·9 t	24·8 t	24·9 t	+0·1	25·9 t	25·9 t	0·0	25·9 t	26·1 t	+0·2
4	26·7 t	26·6 t	26·8 t	+0·2	27·5 t	27·9 t	+0·4	27·6 t	28·0 t	+0·4
5	129·4 d	129·9 d	129·4 d	−0·5	130·4 d	130·3 d	−0·1	130·2 d	130·7 d	+0·5
6	129·1 d	128·7 d	129·0 d	+0·3	130·1 d	126·7 d	−3·5	131·4 d	127·7 d	−3·7
7	25·5 t	25·0 t	24·9 t	−0·1	26·2 t	27·0 t	+0·8	26·3 t	27·0 t	+0·7
8	50·2 d	54·5 d	54·4 d	−0·1	56·1 d	56·1 d	0·0	56·1 d	56·3 d	+0·2
9	72·6 d	69·7 d	69·7 d	0·0	71·7 d	71·1·d	−0·6	71·8 d	71·3 d	−0·5
10	42·9 t	44·1 t	44·1 t	0·0	44·2 t	44·2 t	0·0	44·3 t	44·3 t	0·0
11	77·7 d	71·6 d	71·5 d	−0·1	72·2 d	72·5 d	+0·3	72·3 d	72·5 d	+0·2
12	55·7 d	49·1 d	49·1 d	0·0	50·7 d	50·3 d	−0·4	50·8 d	50·5 d	−0·3
13	132·9 d	132·0 d	131·9 d	−0·1	132·0 d	131·4 d	−0·6	132·0 d	131·4 d	−0·6
14	135·5 d	135·7 d	135·5 d	−0·2	135·9 d	133·4 d	−2·5	136·0 d	134·1 d	−1·9
15	73·2 d	76·0 d	75·9 d	−0·1	77·7 d	77·5 d	−0·2	77·8 d	77·6 d	−0·2
16	37·2 t	37·8 t	37·7t	−0·1	73·3 t	73·2 t	−0·1	73·5 t	73·5 t	0·0
17	25·3 t	25·0 t	24·9 t	−0·1	161·1 s	160·9 s	−0·2	160·6 s	160·6 s	0·0
17	25·3 t	25·0 t	24·9 t	−0·1	161·1 s	160·9 s	−0·2	160·6 s	160·6 s	0·0
18	31·8 t	31·6 t	31·5 t	−0·1	116·1 d	116·1 d	0·0	112·6 d	112·7 d	+0·1
19	22·6 t	22·4 t	22·3 t	−0·1	135·8 s	135·7 s	−0·1	[c]	[c]	—
20	14·0 q	14·1 q	14·1 q	0·0	121·9 d	121·9 d	0·0	118·4 d	118·5 d	+0·1
21	—	—	—	—	131·4 d	131·4 d	0·0	132·0 d	131·9 d	−0·1
22	—	—	—	—	114·1 d	114·1 d	0·0	119·3 d	119·4 d	+0·1

[a] Data taken from ref.[10]; [b] data in hexadeuteriodimethyl sulphoxide; [c] not determined.

matic carbon atoms area of shifts and their assignment is difficult. We solved the problem by means of a heterocorrelated 2D NMR experiment[11]. An analysis of the experiment enabled us both to assign olefinic and aromatic atoms and to correct the assignment of C-9, C-11, and C-15 (or C-8 and C-12) atoms.

In spite of the usually proclaimed stereoselectivity of prostaglandin syntheses, a careful analysis of commercially available compounds *I*–*III* reveals various amounts of isomeric by-products. The most usual of these are $\Delta^{5,6}$-*trans* and 15-epi compounds. It is rather difficult task to monitor analytically these compounds on the 0·1–1% level. The purification of prostaglandins *I*–*III* can be easily accomplished using crystalline complexes *IV*–*VI*. The effect of single-cycle purification procedure is summarized in Table IV for compounds *I* and *II*.

EXPERIMENTAL

Measurements of ^1H and ^{13}C NMR spectra were performed in the FT mode on a Varian XL-200 instrument (200 MHz for ^1H and 50·31 MHz for ^{13}C). The compounds were dissolved in ($^2H_4$)methanol. Solvent peaks $\delta = 3{\cdot}5$ in ^1H NMR and $\delta = 49{\cdot}0$ in ^{13}C NMR were used for chemical shift calculation. HPLC analyses were performed on a Spectra Physics 8000 B Liquid Chromatograph. Compounds *I* and *IV* were treated with 1-bromo-2-acetonaphthone as described in literature[12] and then analysed on a 300 × 3·2 mm column packed with Separon SIX (Laboratorní přístroje, Prague, Czechoslovakia), using n-hexane–dichloromethane–methanol 45 : 55 : 3·5 mixture and UV detection at 254 nm. Compounds *II*, *III*, *V*, *VI* were analysed directly on a 250 × 4 mm column packed with Separon C 18 (Lachema, Brno, Czechoslovakia), using methanol–water–acetic acid 550 : 443 : 7 and UV detection at 274 nm. Prostaglandins *I*–*III* are commercial products (Spolana Neratovice, Czechoslovakia).

Complex $PGF_2 . AgNO_3$ (*IV*)

Crude compound *I*, (179 mg, 0·507 mmol) in 6 ml of ethyl acetate was treated with 0·15 ml of a solution of silver nitrate in acetonitrile (*c* 4 mol l^{-1}) at ambient temperature. The crude oil crystallized out by standing overnight (256 mg). One crystallization from ethanol–ethyl acetate (3 : 2) yielded 143 mg (53%) of a white solid, m.p. 142–150°C (decomp.). For $C_{20}H_{34}AgNO_8$ (524·4) calculated 45·81% C, 5·53% H, 2·67% N; found: 45·52% C, 5·17% H, 2·40% N.

TABLE IV

Single-cycle purification of *I* and *II* using their $AgNO_3$ complexes *IV* and *V* (all data in %)

Compound	*I* → *IV* → *I*		*II* → *V* → *II*	
Parent	97·5	99·6	94·2	97·7
15-Epi	0·5	0·2	0·7	0·3
$\Delta^{5,6}$-*trans*	2·0	0·2	5·0	2·0

Complex Cloprostenol . $AgNO_3$ (*I*)

To 6·0 g (14·1 mmol) of *II* in 25 ml of ethanol, 3·55 ml of a solution of silver nitrate in acetonitrile (*c* 4 mol l^{-1}) was added. The mixture was diluted with 80 ml of ethylacetate, cooled and left overnight. White crystals were separated (6·32 g) and recrystallized from 2-propanol, yielding 5·30 g (64%) of pure *V*, m.p. 85—104°C (decomp.). For $C_{21}H_{27}AgClNO_9$ (594·8) calculated: 44·38% C, 4·88% H, 2·35% N; found: 44·26% C, 5·35% H, 2·19% N.

Complex Fluprostenol . $AgNO_3$ *VI*

2·3 g (5·02 mmol) of fluprostenol *III* was dissolved in 10 ml of ethanol and treated with 1·25 ml of a solution of silver nitrate in acetonitrile (*c* 4 mol l^{-1}). Ethyl acetate–hexane (1 : 1) (5 ml) was gradualy added and mixture was left at ambient temperature for 24 h. The solid was separated (2·22 g), crystallized from ethyl acetate–ethanol (2 : 1), and 1·1 g (35%) of pure *VI* was obtained, m.p. 102—113°C (decomp.). For $C_{22}H_{27}AgClF_3NO_9$ (628·4) calculated: 42·05% C 4·32% H, 2·23% N; found: 41·73% C, 4·07% H, 2·40% N.

Decomposition of Complexes *IV*—*VI*

A solution of the complex (10 mmol) in 30 ml of methanol was treated with 5 ml of a saturated NaCl solution in water. The mixture was stirred for 15 min, silver chloride was filtered off, washed with methanol, and combined filtrates were evaporated *in vacuo*. Pure compounds *I*—*III* were obtained.

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