STEROID DERIVATIVES. LXXV.*

THE PREPARATION OF POLYHALOGENATED DERIVATIVES OF PROGESTATIONAL HORMONES AND THE DETERMINATION OF THEIR CONFORMATION BY CIRCULAR DICHROISM SPECTRA

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4,6-Dihalo derivatives of 17α-acetoxyprogesterone were prepared and the conformation of the rings A and B was determined by means of CD spectroscopy.

Further experiments aimed at obtaining more active derivatives of 17α-acetoxyprogesterone, which were modified in our laboratory earlier, led us to the preparation of 4,6-dihalogenated derivative of this substance.

The described syntheses of 4,6-dichloro-4,6-diene start from 6-chloro-4,6-diene-3-one *Ia* to which chlorine is added using either lithium chloride and N-chlorosuccinimide in acetic acid under catalysis of dry hydrogen chloride (method *A*, ref.[1-3]) or chlorine in tetrachloromethane (method *B*, ref.[3]), affording 4α,6,7α-trichloro derivative *IIa*. Dehydrochlorination of substance *IIa* with pyridine affords the required 4,6-dichloro-4,6-dien-3-one *IIIa*. A further possibility consists in the so called "direct chlorination" with chlorine in propionic acid and dimethylformamide (method *C*, ref.[3]).

Our aim was to prepare 4,6-dichloro- and 4-chloro-6-bromoanalogues of "superlutin" (17α-acetoxy-16-methylene-4,6-pregnadiene-3,20-dione) *IIIc* and *IIId*. The described reactions do not take place in these cases unambiguously and the yields are rather variable. With the described 6-chloro-4,6-diene *Ia* we had already obtained, by application of method A, 4α,6,7α-trichloro derivative *IIa* which contained substances of a higher chlorine content as impurities. With respect to low stability of the trichloro derivative, and still greater instability of the higher chlorinated by-products, we were unable to isolate them. When chromatographing crude trichloro derivative *IIa* on silica gel we obtained an unidentified mixture of decomposition products, and only a small proportion (approx. 20%) of trichloro derivative *IIa*. With pyridine the latter gave pure 4,6-dichloro-4,6-pregnadiene (*IIIa*) almost quantitatively, while the crude product gave, after the same reaction, a mixture of several

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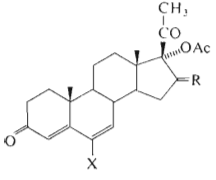
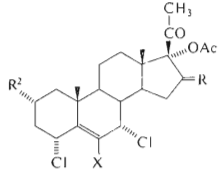
compounds of which the two main ones could be separated chromatographically on silica gel. On elution with benzene 2α,4,6-trichloro derivative *IIIe* was obtained the structure and configuration of which was determined on the basis of the NMR spectrum which contained a doublet of doublets at 4·82 p.p.m. typical of the pseudo-axial hydrogen at $C_{(2)}$ of the 4,6-dichloro-4,6-dien-3-one grouping. Elution with benzene–chloroform (3 : 1) afforded the required 4,6-dichloro-4,6-diene *IIIa* the physical constants of which were in agreement with the literature[1–3]. On subsequent dehydrochlorination with calcium carbonate in dimethylformamide the trichloro derivative *IIIe* gave 4,6-dichloro-1,4,6-triene *IV* with a characteristic UV and NMR spectrum.

The presence of these two dehydrohalogenation products indicates that originally addition of chlorine and substitution with chlorine in the position $C_{(2)}$ took place simultaneously, which was enabled by the strongly acidic medium in which the 3-oxo group enolised to position 2-3. The result of the reaction differed only little after application of different methods, and the difference was rather quantitative than



I



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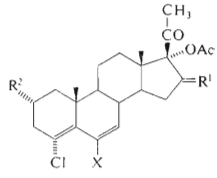


III

Ia; X = Cl, R = 

Ib; X = Br, R = 

Ic; X = Cl, R = =CH_2

Id; X = Br, R = =CH_2

IIIa; X = Cl, R^1 =  , R^2 = H

IIIb; X = Br, R^1 =  , R^2 = H

IIIc; X = Cl, R^1 = =CH_2, R^2 = H

IIId; X = Br, R^1 = =CH_2, R^2 = H

IIIe; X = Cl, R^1 =  , R^2 = Cl

IIa; X = Cl, R^1 =  , R^2 = H

IIb; X = Br, R^1 =  , R^2 = H

IIc; X = Cl, R^1 = =CH_2, R^2 = H

IId; X = Br, R^1 = =CH_2, R^2 = H

Ac = CH_3CO

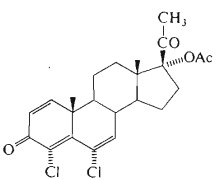
IIe; X = Cl, R^1 =  , R^2 = Cl

SCHEME 1

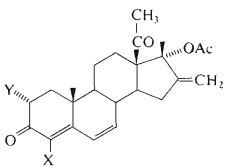
qualitative. Method *B* was relatively milder and alone afforded positive results with analogues *Ic* and *Id*, where the reaction is complicated by the presence of 16-exo-methylene group, *i.e.* of an additional reactive center. Hence, using the method *B*, 6-bromo-4,6-diene-3-oxo derivative *Ib* (ref.[4]) was transformed to 6-bromo-4α,7α-dichloro derivative *IIb* which on reaction with pyridine gave 6-bromo-4-chloro-4,6-diene *IIIb* in a 32% yield. Similarly, from 6-chloro-4,6-diene and 6-bromo-4,6-diene of the 16-methylene series (*Ic* and *Id*; ref.[5]) trichloro derivative *IIc* and 6-bromo-4α,7α-dichloro derivative *IId*, and 4,6-dichloro-4,6-diene *IIIc* and 6-bromo-4-chloro-4,6-diene *IIId* have been obtained which, however, had to be purified chromatographically on silica gel before crystallisation. The total yields were approximately half of those of 16-unsubstituted derivatives *IIIa* and *IIIb*.

In Table I the comparison of the chemical shift values of some protons in the NMR spectra of these substances with those of substances containing only a single halogen in the A or B ring is given.

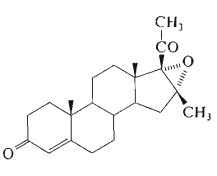
From Table I it is evident that the values of the prepared substances (*IIIb*, *IIIc*, *IIId* and their intermediates *IIc* and *IId*) are in good agreement with the values from the literature[3] (substance *IIIa* or *IIa*). Further, the effect of the substitution of bromine for chlorine at $C_{(6)}$ is also proved. Similarly as in the starting compounds *Ic* and *Id* this substitution also causes a downfield shift of the proton signal at $C_{(7)}$ by approx.



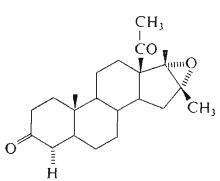
IV



Va; X = H, Y = H
Vb; X = Cl, Y = H
Vc; X = H, Y = Cl

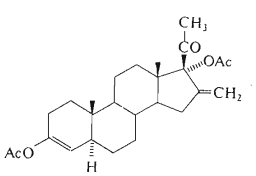


VI

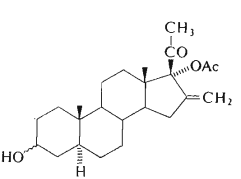


VII

Ac = CH_3CO



VIII



IX

TABLE I

Chemical Shifts of Some Protons (δ, p.p.m.) in PMR Spectra

Substance	$C_{(4)}$	$C_{(7)}$	$C_{(19)}$
Ic	6·36 s (1 H)	6·35 d (1 H)	1·15 s (3 H)
Id	6·35 s (1 H)	6·60 d (1 H)	1·15 s (3 H)
IIIa	—	6·34 d (1 H)	1·20 s (3 H)
IIIb	—	6·60 d (1 H)	1·21 s (3 H)
IIIc	—	6·30 d (1 H)	1·19 s (3 H)
IIId	—	6·60 d (1 H)	1·19 s (3 H)
IIa	4·82 s (1 H)	4·44 d (1 H)	0·90 s (3 H)
IIc	4·85 s (1 H)	4·46 d (1 H)	0·92 s (3 H)
IId	4·81 s (1 H)	4·55 d (1 H)	0·91 s (3 H)
IIIe[a]	—	6·36 d (1 H)	1·29 s (3 H)
IV[b]	—	6·19 d (1 H)	1·29 s (3 H)
Vb	—	[c]	1·14 s (3 H)

[a] $C_{(2)}$: 4·82 dd (1 H) pseudoax.; [b] $C_{(1)}$—$C_{(2)}$: *AB*q 7·08 d, 6·34 d (2 H); [c] $C_{(4)}$—$C_{(7)}$: *AB*q 6·82 d, 6·23 d.

0·3 p.p.m. in the pairs *IIIa*, *IIIb*, and *IIIc*, *IIId*. Finally a small downfield shift of the proton signal at $C_{(19)}$ of dihalo derivatives *IIIa*–*IIId* is also observed, in contrast to the starting monohalo derivatives.

For circular dichroism measurements 4-chloro-4,6-diene-3-one *Vb* and 2α-chloro--4,6-diene[6] *Vc* were also prepared; their UV, IR and NMR spectra agreed well with the supposed structure. We also prepared 17α-acetoxy-3ξ-hydroxy-16-methylene--5α-pregnane-20-dione (*IX*) by the following reaction sequence: 16β-methyl-16α,17α-epoxide *VI* was hydrogenated in ethyl acetate under catalysis with Pd/Al_2O_3 to the 5α-saturated derivative *VII* the epoxide ring of which was opened with acid[7] to afford 17α-acetoxy-16-methylene derivative *VIII* and the latter was reduced with sodium boro-hydride in methanol[8] to the required compound *VIII* which contained only a single chromophore in the D ring. Here too the IR and NMR spectra were in agreement with the supposed structure.

The conformation of the A and B rings of the starting 6-chloro-4,6-diene *Ia* was determined by Snatzke[9] on the basis of the CD band of maximum wave length, and the conformation of 4α,6,7α-trichloro derivative *IIa* was determined by Kierstead and coworkers[3] on the basis of NMR spectra and X-ray analysis. A and B rings in 6-chloro-4,6-diene *Ia* assume a planar arrangement from $C_{(2)}$ to $C_{(7)}$ and $C_{(1)}$ determines the sign of the Cotton effect; in trichloro derivative *IIa* the A ring occurs in boat conformation. From NMR (Table I) and CD data (Table II) it follows that the conformations of analogous *Ib,c,d* and *IIc,d* are the same. The conformation

TABLE II

Parameters of Circular Dichroism Spectra; λ_{max} ($\Delta\varepsilon$)

No	1.	2.	3.	4.	5.	6.[a]
Ia	355, 345 (+2·2; +2·2)	300 (+ 4·3)	272 (−1·3)	250 (−5·6)	225, 210 (−3·1; −2·8)	195 (0)
Ic	353 (+2·8)	302 (+ 3·4)	273 (−1·6)	257, 242 (−4·5; −5·4)	211 (− 1·1)	200 (−11·0)
Id	352 (+2·2)	300 (+ 1·2)	270 (−5·4)	250 (−5·4)	209 (− 0·6)	200 (− 1·6)
Vb	341 (+4·9)	315 (+ 2·1)	283 (−4·9)	260, 245, 232 (−2·2; −1·8; −0·7)	213 (− 5·3)	200 (−17·0)
Vc	343 (+2·8)	318, 301 (+1·1; +1·8)	275 (−3·5)	260, 250 (−2·1; −1·8)	223 (+ 0·8)	200 (−10·0)
X	342 (+3·1)	304 (+ 2·0)	272 (−6·5)	250 (−2·9)	236, 222 (−2·1; −1·2)	200 (− 4·4)
XI	342 (+3·6)	300 (+ 1·2)	275 (−7·5)	250 (− 3·0)	220 (− 0·7)	200 (−10·0)
IX	—	292 (+ 1·0)	—	—	211 (+ 0·6)	200 (− 6·5)
IIIa	341 (−2·5)	301 (+21·2)	275, 265 (+6·7; +3·6)	253 (+1·8)	205 (−19·2)	190 (+15·4)
IIIb	341 (−1·6)	303 (+12·6)	275 (+5·6)	235 (−2·0)	209 (−11·0)	195 (− 6·0)
IIIc	340 (−2·5)	300 (+19·3)	270, 260 (+2·7; +1·3)	—	210 (−15·0)	—
IIId	343 (−3·0)	304 (+20·6)	274 (+8·2)	233 (−6·8)	210 (−18·4)	—
IIIe	345 (−2·5)	305 (+20·0)	275 (+4·7)	250 (+0·6)	205 (−20·3)	—
IIc	340 (−0·6)	301 (+ 4·4)	—	241 (−3·6)	228 (− 2·6)	200 (−13·6)
IId	342 (−0·7)	301 (+ 9·8)	270 (+2·7)	—	230 (− 2·7)	200 (−13·2)

[a] Final measured value with the exception of compound *IX*: final value 195 (−1·0).

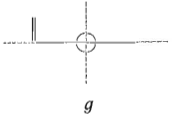
of dihalogeno derivatives *IIIa–IIId* remains questionable *i.e.* it is not clear what effect the introduction of the second halogen atom (chlorine) in the position 4 has on the conformation of the rings A and B and how the existence of the second chromophore (ring D) manifests itself on the CD curve. Therefore the spectra were measured in a maximum range of wave-lengths. The results are summarized in Table II. Substances *X* and *XI* are 4,6-dien-3-ones described, for example, by Syhora and coworkers[5].

The spectra of substances *Ia*, *Ic*, *Id*, *Vb*, *Vc* and *XI* are very similar as regards the position and the sign of the Cotton effects and the ε values. The following dichroitic bands are evident: *1.* a positive one at 340–343 nm, for substances unsubstituted at $C_{(4)}$ and $C_{(6)}$ or substituted only at one of these atoms, which is shifted to longer wave-lengths in substances substituted in the position 6 only. In accordance with Snatzke[9] the band of 6-halogen derivatives *Ic*, *Id* is a little less strong than in substance without a halogen substituent in the position 6; *2.* a positive one at 300 nm of a comparable intensity with the preceding one; *3.* a negative one, rather strong, at 275 nm, with a slight bathochromic shift in the case of substance *Vb*; *4.* a negative one at 250 nm, very poorly detectable; *5.* a positive band at 210–220 nm; in the majority of substances it is visible on the curve as a negative minimum with a very low Δε value; only in the case of substance *Vc* it attains a true positive value, in substance *Vb* it is shifted bathochromically; *6.* in the region about 200 nm a strong negative dichroitic absorption was detected in all substances, but a minimum was never attained. The values found for the first band may be compared with the data given[9] for 17β-hydroxy--4,6-androstadien-3-one and 17α-acetoxy-6-chloro-4,6-pregnadiene-3,20-dione. Evidently, the cycles containing a conjugated unsaturated system have in all substances the same configuration on atoms $C_{(2)}$ to $C_{(7)}$ occuring on one plane and the direction of the long-wave Cotton effect follows from the position of the $C_{(1)}$ atom. The agreement of further dichroitic bands shows that on substitution with one halogen atom other dichroitic electronic transitions which must also be necessarily connected with the dienone system are not affected either. Comparison with substances *Vb* and *X* shows that substituents on ring D do not play an important role in the modelling of the dichroitic curves. Probably only the positive bands at 210 and 300 nm could depend on the electronic transitions in this part of the molecule. In this region the spectrum of substance *IX* (without the dienone grouping in the rings A and B) has a very similar shape, but the dichroitic absorption in the carbonyl region is substantially less intensive in this substance than in the substances discussed above. The course of the CD curve of the dienone system is not significantly affected and nor is the conformation either by the nature of the single halogen atom or its position at $C_{(4)}$ or $C_{(6)}$. The observed small changes in compound *Vb* with a chlorine atom in the position 4 cannot be considered as significant. In contrast to this distinct change of the curve is observable in substances with two halogen atoms in positions 4 and 6. Substances *IIIa–IIIe* have: *1.* the dichroitic band of the longest wave of the

opposite sign (negative); *2.* the Cotton effect has its positive sign preserved but its intensity is enormously increased ($\Delta\varepsilon$ 10 – 20); *3.* in contrast to monohalogen derivatives the Cotton effect is positive; *4.* the Cotton effect is detectable with difficulty, it is visible as a distinct band only in bromo derivatives *IIIb* and *IIId*; *5.* the dichroitic band of the shortest wave is intensive, negative, and localised at 200 – 210 nm. In no instance could a maximum be attained.

The changed parameters of the dichroitic bands show that a change of spacial arrangement took place. In view of the appreciable volume of the two halogen atoms at $C_{(4)}$ and $C_{(6)}$ the dienone system evidently can no longer be arranged planarly but it forms a helical segment. The conformation best suiting the given structure according to Dreiding models has its A ring in semi-chair conformation and it may be identified with the projection *g* given by Snatzke[10]. A negative Cotton effect in the longest wave region is supposed for it. This conformation does not disagree with the results of the PMR spectroscopy either. From the comparison of the δ values of chemical shifts of the $C_{(19)}$-methyl protons of 4-en-3-ones (1,2), 4,6-dien-3-ones (1,1-1,2) ref.[11]), 4-chloro-4,6-dien-3-one *Vb* (1,14), 6-chloro-4,6-dien-3-one *Ic* (1,15), and 4,6-dichloro-4,6-dien-3-one *IIIc* (1,19) it is evident that *a*) the substitution with one halogen in the positions 4 or 6, or *b*) the substitution with 2 halogens in the positions 4 and 6 has only a weak effect on the chemical shift of the $C_{(19)}$ methyl protons, and therefore it may be judged that the conformation of the rings A and B is either planar in the case *a*) or that the ring A in the case *b*) occurs in semi-chair conformation close to the conformation of 4-en-3-ones. The semi-boat conformation of the ring A (*i.e.* the second alternative according to Dreiding models), similar to the conformation of 5α-H-3-oxo derivatives, should be characterized by a similar diamagnetic shift of the $C_{(19)}$ protons, caused by the shielding effect of the 3-oxo group on the $C_{(19)}$ methyl (approx. 1·0) (ref.[12]).

The CD curves of trihalogeno derivatives *IIIc* and *IIId* have again a negative Cotton effect at longest wave lengths which is in agreement with the supposed[3] boat conformation and the projection *d* with the negative Cotton effect given by Snatzke[10].



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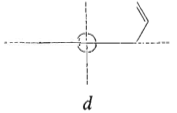

d

It seems that the deformation of the rings A and B could manifest itself by a long-range effect even on the chromophore of the D ring substituents. Under the supposition that the dichroitic band at 300 nm is really due to the $n \rightarrow \pi^*$ electron transitions in the carbonyl group at $C_{(20)}$, its appreciably increased intensity would thus be rationalised. Such a long-range effect over the whole molecule is not impossible, as

was found by Schwarz and coworkers[13] during the addition of bromine to the Δ^5 (ref.[5]) double bond of steroids with various substituents at $C_{(17)}$. Pharmacological testing of the activity of dihalogeno derivatives *IIIa* to *IIIc* did not reveal any distinct increase in gestagenic activity in comparison with the original monohalogeno derivatives *Ia* and *Id*.

EXPERIMENTAL

Melting points were determined on a Kofler microblock. Optical rotations were measured in chloroform unless stated otherwise, with a $\pm 3°$ precision. Samples for analysis were dried over phosphorus pentoxide at 0·01 Torr for 24 hours. Ultraviolet spectra were measured on a Zeiss model VSU-1 spectrophotometer (NaCl prisms, quartz cell 1 cm thick) in methanol. Infrared spectra were measured on a two-beam spectrophotometer Zeiss, model UR-10, in 6% chloroform solutions. PMR spectra were measured on a Zeiss ZKR 60 MHz apparatus in deuteriochloroform, using tetramethylsilane as internal reference. Circular dichroism spectra were measured on Dichrographe Jouan UV 185/II in methanol, concentration 0·05 g/100 ml, cells 0·05–0·1 cm. Thin-layer chromatography was carried out on Kieselgel GF 254 according to Stahl in benzene–ethyl acetate 9 : 1. Column chromatography was carried out on silica gel Silpearl (Kavalier, Votice).

Chlorination of 17α-Acetoxy-6-chloro-4,6-pregnadiene-3,20-dione (*Ia*)

Method A: 2 g of 6-chloro-4,6-diene *Ia* were chlorinated with 0·5 g of lithium chloride and 1·65 g N-chlorosuccinimide in 30 ml of acetic acid and 0·1 ml of a saturated hydrogen chloride solution in dioxan. Working up of the reaction mixture (see[1]) gave a residue (2·54 g) which was dissolved in 3·6 ml of pyridine and allowed to stand at room temperature for 2 h. It was diluted with approx. 100 ml of ether, extracted four times with 25 ml portions of 0·5M-H_2SO_4, three times with 5% sodium hydrogen carbonate solution, and water until neutral. After drying with magnesium sulfate and filtration ether was evaporated under reduced pressure. The residue (1·897 g) was chromatographed on 50 g od silica gel. Elution with benzene gave 0·485 g (21%) of trichloro derivative *IIIa* which on crystallisation from methanol gave an analytically pure sample, m.p. 230–236°C; $[\alpha]_D^{20}$ +113°. UV spectrum: λ_{max} 304 (log ε 4·20) nm. Ir spectrum: 1720, 1260, 1021, (CH_3COO), 1705 (C_{20}=O and conjugated C=O), 1354 (CH_3CO), 1598, 1550 (conj. C=O) cm^{-1}. PMR: 0·71 s, 3 H (C_{18}—H_3), 1·26 s, 3 H (C_{19}—H_3), 2·04 s, 3 H (CH_3COO), 2·09 s, 3 H, ($COCH_3$), 6·36 d J = 2·5 Hz ($C_{(7)}$H), 4·82 dd, 1 H, J_1 = 6·0 Hz, J_2 = 14·0 Hz ($C_{(2)}$—H pseudoax.). For $C_{23}H_{27}Cl_3O_4$ (473·8) calculated: 58·29% C, 5·75% H, 22·45% Cl; found: 58·33% C, 5·72% H, 22·32% Cl. Using a benzene–chloroform mixture (3 : 1) 0·8 g (39%) of 4,6-dichloro-4,6-diene *IIIa* were eluted, m.p. 205–207°C, the m.p., UV, IR and PMR values of which coincided with literature data[3]. In a further experiment (2 g of substance *Ia* were chlorinated) the crude residue (2·62 g) was chromatographed on silica gel. Elution with benzene and light petroleum (1 : 1) gave 452 mg (19%) of trichloro derivative *IIa*, corresponding to literature data[3]. This trichloro derivative gave on reaction with pyridine 405 mg (97%) of dichloro derivative *IIIa*.

Method B: To a solution of 2 g of 6-chloro-4,6-diene *Ia* in 7 ml of chloroform a 1M solution of chlorine in tetrachloromethane (1·15 ml) was added over 10 min. After 30 minutes standing the reaction mixture was evaporated to dryness and the residue triturated three times with n-heptane and then dried in a vacuum. The residue (2·4 g) when crystallised from a mixture of ethyl acetate and cyclohexane gave 1·8 g (80%) of trichloro derivative *IIa* the physical constants of which

agreed with the literature[3]. After dissolution in pyridine (5 ml) and two hours standing it was worked up in the above described manner. The residue (1·56 g) was crystallised from a mixture of dichloromethane and ether affording 1·4 g (67%) of dichloro derivative *IIIa*.

Method C: To a solution of 2 g of 6-chloro-4,6-diene *Ia* in 10 ml of ether and 20 ml of dimethylformamide 16 ml of a 0·32M chlorine solution in propionic acid were added at −5°. After 20 minutes standing at +5°C the mixture was poured into 150 ml of water, extracted into a mixture of ether and dichloromethane (3 : 1), and the organic layer washed with a 5% sodium hydrogen carbonate solution and water until neutral, then dried over magnesium sulfate and evaporated *in vacuo*. The residue (2·56 g) was chromatographed on silica gel under the above given conditions, affording 0·453 g (20%) of trichloro derivative *IIIe* and 1·3 g (63%) of dichloro derivative *IIIa*.

17α-Acetoxy-6-bromo-4-chloro-4,6-pregnadiene-3,20-dione (*IIIb*)

To a solution of 0·5 g of 6-bromo-4,6-diene *Ib* in 7 ml of chloroform 1·18 ml of a 1M chlorine solution was added over 10 min. After 30 min standing the reaction mixture was worked up as described above and the residue (0·65 g) was dissolved in 1·5 ml of pyridine. After two hours standing the solution was worked up as above. Yield 0·462 g (86%) of 6-bromo-4-chloro-4,6-diene *Vb*, m.p. 239—245°C, which on crystallisation from methanol afforded an analytically pure sample: m.p. 243—244°C, $[\alpha]_D^{20}$ +136°. UV spectrum: λ_{max} 305 (log ε 4·14) nm, IR spectrum: 1725, 1260, 1020 (CH_3COO), 1708 ($C_{(20)}$=O), 1356 (CH_3CO), 1685, 1592, 1550 (conj. C=O) cm^{-1}. PMR: 6·60 d, 1 H, ($C_{(7)}$—H), 2·04 s 3 H (CH_3COO), 2·09 s, 3 H ($C_{(21)}$—H_3), 0·70 s, 3 H (C_{18}—H_3), 1·21 s, 3 H (C_{19}—H_3); for $C_{29}H_{28}BrClO_4$ (483·8) calculated: 57·09% C, 5·83% H, 16·52% Br; 7·33% Cl, found: 57·34% C, 6·09% H, 16·62% Br, 7·45% Cl.

17α-Acetoxy-4,6-dichloro-1,4,6-pregnatriene-3,20-dione (*IV*)

A solution of 300 mg of trichloro derivative *IIIe* in 3 ml of dimethylformamide was additioned with 100 mg of calcium carbonate and refluxed for 3 h. The undissolved material was filtered off and the filtrate evaporated. The residue (approx. 250 mg) was crystallised from methanol, (220 mg, 80%) m.p. 230—232·5°C, $[\alpha]_D^{20}$ +25·5°. UV spectrum: λ_{max} 235 (log ε 4·09), 306 (log ε 3·93) nm. IR spectrum: 1721, 1260, 1021 (CH_3COO), 1710 ($C_{(20)}$=O) 1356 ($COCH_3$), 1660, 1635, 1600, 1561, 830, 839 ($\Delta^{1,4,6}$—$C_{(3)}$=O) cm^{-1}. PMR: 0·71 s, 3 H (C_{18}—H_3), 1·29 s, 3 H (C_{19}—H_3), 2·08 s, 3 H (C_{21}—H_3), 2·06 s, 3 H (CH_3COO), 6·19 d, (J = 3·0 Hz, 1 H ($C_{(7)}$—H), 7·08, 6·46 d J = 11 Hz AB-quartet, 2 H (C_1H=C_2H). For $C_{23}H_{28}Cl_2O_4$ (437·35) calculated: 63·15% C, 5·99% H, 16·21% Cl; found: 63·28% C, 6·08% H, 16·39% Cl.

17α-Acetoxy-16-methylene-4α,6,7α-trichloro-5-pregnene-3,20-dione (*IIc*)

To a solution of 2·5 g of 6-chloro-4,6-diene *Ic* in 35 ml of chloroform a solution of 0·8 g of chlorine in 12·5 ml of tetrachloromethane was added over 10 min at 0°C and the mixture was allowed to stand for 30 min. It was worked up in the above described manner. Crystallisation of the residue (2·9 g) from ethyl acetate–cyclohexane mixture gave 1·8 g (61·6%) of trichloro derivative *IIc*, m.p. 161—163°C. A sample for analysis was crystallised in the same manner, m.p. 184—190°C, $[\alpha]_D^{20}$ −114°. UV spectrum: λ_{max} 243 (log ε 3·68), 291 (log ε 3·79) nm. IR spectrum: 1730, 1710 ($COCH_3$, $C_{(20)}$=O), 1356 ($COCH_3$). PMR: 5·49, 5·63, 2 H (16-exomethylene), 4·85 s 1 H ($C_{(4)}$—H), 4·46 d 1 H ($C_{(7)}$—H), 2·05 s, 3 H (CH_3COO), 2·12 s, 3 H (C_{21}—H_3), 0·71 s, 3 H (C_{18}—H_3), 0·92 s, 3 H (C_{19}—H_3). For $C_{24}H_{29}Cl_3O_4$ (487·8) calculated: 59·09% C, 5·99% H, 21·81% Cl; found: 59·10% C, 6·36% H, 21·36% Cl.

17α-Acetoxy-6-bromo-4α,7α-dichloro-16-methylene-5-pregnene-3,20-dione (*IId*)

A solution of chlorine (0·95 g) in 13 ml of tetrachloromethane was added dropwise over 15 min to a solution of 2·8 g of 6-bromo-4,6-diene *Id* in 35 ml of chloroform, kept at 0°C. After 50 min reaction the mixture was worked up in the above described manner and the residue (3·2 g) crystallised from a mixture of ethyl acetate and cyclohexane. Yield 1·69 g (52%) of trihalogeno derivative *IId*, m.p. 193–199°C. A sample for analysis was crystallised from the same solvents: m.p. 208 to 210°C; $[\alpha]_D^{20}$ −152°. UV spectrum: λ_{max} 247 (log ε 3·63) nm; IR spectrum: 1722, 1259, 1020 (CH_3COO), 1808 ($C_{(20)}$=O), 1356 ($COCH_3$) cm^{-1}. PMR: 5·62, 5·50, 2 H (16-exomethylene), 4·55 d, 1 H ($C_{(7)}$—H), 4·81 s 1 H ($C_{(4)}$—H), 2·05 s 3 H (CH_3COO), 2·13, 3 H ($C_{(21)}$—CH_3), 0·70 s, 3 H (C_{18}—H_3), 0·91, 3 H (C_{19}—H). For $C_{24}H_{29}BrCl_2O_4$ (532·3) calculated: 54·1% C, 5·79% H, 15·02% Br, 13·32% Cl; found: 54·59% C, 5·49% H, 15·85% Br, 12·96% Cl.

17α-Acetoxy-4,6-dichloro-16-methylene-4,6-pregnadiene-3,20-dione (*IIIc*)

a) A solution of 350 mg of crystalline trichloro derivative *IIc* in 1·5 ml of pyridine was allowed to stand at room temperature for 2 h and then diluted with approx. 100 ml of ether and worked up in the above described manner. The residue (0·28 g) was crystallised from methanol, affording 0·238 g (74%) of dichloro derivative *IIIc* of m.p. 198–200°C. A sample for analysis was crystallised from the same solvent: m.p. 208–221°C, $[\alpha]_D^{20}$ −11°. UV spectrum: λ_{max} 299 (log ε 4·6) nm. IR spectrum: 1730, 1260, 1020 (CH_3COO), 1703 ($C_{(20)}$=O), 1356 ($COCH_3$), 1685, 1599, 1550 (conjugated C=O) cm^{-1}. PMR: 6·30 d, 1 H ($C_{(7)}$—H), 5·61, 5·50, 2 H (16-exomethylene), 2·03 s, 3 H ($OCOCH_3$), 2·10 s, 3 H ($C_{(21)}$—CH_3), 0·74 s, 3 H (C_{18}—H_3), 1·19 s, 3H (C_{19}—H_3). For $C_{24}H_{28}Cl_2O_4$ (451·4) calculated: 63·87% C, 6·25% H, 15·71% Cl; found: 64·01% C, 6·30% H, 15·53% Cl.

b) In a control experiment 2 g of trichloro derivative *IIc* (non-crystallised residue) were dissolved in 5·5 ml of pyridine and worked up in the described manner. The residue (1·54 g) was chromatographed on 45 g of silica gel. On elution with benzene with 5% ethyl acetate a fraction was obtained which corresponded to dichloro derivative *IIIc* (0·99 g, m.p. 190–198°C, 53%).

17α-Acetoxy-6-bromo-4-chloro-16-methylene-4,6-pregnadiene-3,20-dione (*IIId*)

A solution of 500 mg of dichlorobromo derivative *IId* (non-crystallised residue) in 5 ml of pyridine was allowed to stand at room temperature for 2 h and then diluted with ether and worked up in the described manner. The residue (0·385 g) was chromatographed on 15 g of silica gel. On elution with benzene containing 5% of ethyl acetate 0·197 g of a fraction were obtained which on crystallisation from methanol afforded 0·15 g (32%) of chlorobromo derivative *IIId*, m.p. 200–212°C. A sample for analysis was crystallised from the same solvent, m.p. 216–218°C, $[\alpha]_D^{20}$ +14°. UV spectrum: λ_{max} 301 nm (log ε 4·19). IR spectrum: 1730, 1260, 1020 (CH_3COO) 1702 ($C_{(20)}$=O), 1356 ($COCH_3$), 1685, 1590, 1550 (conjug. C=O) cm^{-1}. PMR: 6·60 d, 1 H ($C_{(7)}$—H), 5·65, 5·51, 2H (16-exomethylene), 2·03 s, 3 H (CH_3COO), 2·10 s, 3 H (C_{21}—H_3), 0·74 s, 3 H (C_{18}—H_3), 1·19 s, 3 H (C_{19}—H). For $C_{24}H_{28}BrClO_4$ (495·8) calculated: 58·22% C, 5·70% H, 16·15% Br, 7·16% Cl; found: 58·32% C, 5·60% H, 16·22% Br, 6·96% Cl.

17α-Acetoxy-2α-chloro-16-methylene-4,6-pregnadiene-3,20-dione (*Vc*)
and 17α-acetoxy-4-chloro-16-methylene-4,6-pregnadiene-3,20-dione (*Vb*)

To a solution of 5·1 g of dienone *Va* in 200 ml dioxan and 20 ml of water 2·1 g of N-chlorosuccinimide and 1·2 ml of 70% perchloric acid were added and the mixture stirred at room tempera-

ture for 16 hours. It was poured into 2·5 l of water and the precipitate was filtered off under suction and washed until neutral. The dry product (4·5 g) was chromatographed on 450 g of silica gel. Elution with benzene gave 0·88 g (16%) of a fraction which on crystallisation from diisopropyl ether gave 2α-chloro-4,6-diene *Vc* (0·79 g, 14%), m.p. 210–213°C, $[\alpha]_D^{20}$ −69°. UV spectrum: λ_{max} 288 nm (log ε 4·39). PMR: 6·25 s, 2 H, 5·87 s, 1 H (C_4—H, C_6—H, C_7—H), 5·67, 5·55, 2 H (16-exomethylene), 4·48 dd, J_{ae} = 5·0 Hz, J_{aa} = 12·0 Hz, ($C_{(2)}$—H), 2·08 s, 3 H (CH_3COO), 2·18 s, 3 H (C_{21}—H_3), 0·80 s, 3 H (C_{18}—H_3), 1·25 s, 3 H (C_{19}—H_3). For $C_{24}H_{29}ClO_4$ (416·9) calculated: 69·13% C, 7·01% H, 8·50% Cl; found: 68·98% C, 7·23% H, 8·82% Cl. Using benzene with 20% ethyl acetate 1·24 g (22%) of 4-chloro-4,6-diene *Vb* were eluted, of m.p. 238–240°C, a sample of which also was crystallised from diisopropyl ether: m.p. 240–242°C, $[\alpha]_D^{20}$ −77°. UV spectrum: λ_{max} 295 nm (log ε 4·37). IR spectrum: 1730, 1260, 1021 (CH_3COO), 1708 ($C_{(20)}$=O), 1353 ($COCH_3$), 1670, 1608, 1580 (conjug. C=O) cm^{-1}. PMR: ABq 6·82 d, 1 H, 6·23 d, 1 H, $J_{6,7}$ = 10·0 Hz ($C_{(6)}$,$C_{(7)}$—H), 5·56, 5·46 s, 2 H (16-exomethylene), 2·10 s, 3 H (C_{21}—H_3), 2·01 s, 3 H (CH_3COO), 0·76 s, 3 H (C_{18}—H_3), 1·14 s, 3 H (C_{19}—H_3). For $C_{24}H_{26}ClO_4$ (416·9) calculated: 69·13% C, 7·01% H, 8·50% Cl; found: 69·21% C, 7·30% H, 8·53% Cl.

16α,17α-Epoxy-16β-methyl-5α-pregnan-3,20-dione (*VII*)

A solution of 5 g of 4-pregnen-3-one (*VI*) in 40 ml of acetic acid was hydrogenated on Pd/Al_2O_3 catalyst (1·5 g) until the absorption of hydrogen ceased (5 h, consumption 339·5 ml); the catalyst was filtered off, the mixture poured into 800 ml of water, and the precipitated material was washed until neutral. After drying it was crystallised from methanol. Yield 4·51 g of saturated epoxide *VII*, m.p. 175–180°C, $[\alpha]_D^{20}$ +84°; PMR: 2·20 s, 3 H (C_{21}—H_3), 1·44 s ($C_{(16)}$—H_3), 1·02 s, 3 H (C_{19}—H_3). For $C_{22}H_{32}O_3$ (344·8) calculated: 76·70% C, 9·36% H; found: 76·46% C, 9·12% H.

3,17α-Diacetoxy-16-methylene-3-5α-pregnen-20-one (*VIII*)

A solution of 4 g of epoxide *VII* in 50 ml of toluene and 5 ml of acetic anhydride was refluxed under addition of 20 mg of sulfosalicylic acid for 4 h. Simultaneously 18 ml of solvent was distilled off slowly. After addition of 0·1 ml of pyridine the reaction mixture was evaporated, diluted with approx. 50 ml of ethyl acetate, extracted with water, 5% sodium hydrogen carbonate and water until neutral, then dried over magnesium sulfate and evaporated to dryness. The residue (5·1 g) was crystallised from methanol. Yield 4·01 g of 16-methylene derivative *VIII* (80%), m.p. 153–160°C, $[\alpha]_D^{20}$ −66°. PMR: 5·60, 5·45 s, 2 H (16-exomethylene), 5·14 s, 1 H ($C_{(4)}$—H), 2·13 s, 3 H (C_{21}—H_3), 2·10 s, 3 H (CH_3COO), 0·66 s, 3 H (C_{18}—H_3), 0·98 s, 3 H (C_{19}—H_3). For $C_{26}H_{36}O_5$ (428·55) calculated: 72·86% C, 8·47% H; found: 72·59% C, 8·35% H.

17α-Acetoxy-3ξ-hydroxy-16-methylene-5α-pregnan-20-one (*IX*)

A solution of 3·5 g of enol acetate *VIII* in 200 ml of methanol was reduced with 3·5 g of sodium borohydride at room temperature for 1 h. The mixture was poured into 2 l of water and the separated precipitate was washed until neutral. After drying (3·1 g) it was chromatographed on a column of 300 g of silica gel. Elution with benzene gave 2·33 g of a fraction, m.p. 185–195°C, corresponding to 16-methylene derivative *IX*. The sample for analysis was crystallised from ether, m.p. 192–198°C, $[\alpha]_D^{20}$ −77·6°. IR spectrum: 3450, 3590, (OH), 1722, 1260, 1018 (CH_3COO), 1705 ($C_{(20)}$=O), 1353 ($COCH_3$) cm^{-1}. PMR: 5·58, 5·48 s (16-exomethylene), 2·07 s (C_{21}—CH_3, CH_3COO), 0·62 s, 3 H (C_{18}—H_3), 0·90 s, 3 H, (C_{19}—H_3). For $C_{24}H_{36}O_4$ (388·5) calculated: 74·19% C, 9·34% H; found: 73·96% C, 9·07% H.

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