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CIRCULAR DICHROISM OF SOME PREGNENES SUBSTITUTES AT C-17

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Abstract—The optical properties of pregnenes containing different substituents at C-17 (—SCN, —SAc, —$SC(CH_3)_2O$—, —Br, —OAc, —N_3) have been investigated with the help of the CD spectra. It is shown that the sign and value of the Cotton effect of the carbonyl chromophore $n \to \pi^*$ transition is determined by the nature of the substituent at C-17.

Application of the octant rule for the 20-carbonyl chromophore of the 17-acetylsteroids is recognized. Empirical dependence has been obtained which correlates the sign and value of the Cotton effect with the configuration of the 16-substituted pregnanes and isopregnanes.[1,2] The nature of the substituent adjacent to the chromophore has a great influence on the sign and value of the Cotton effect.[1,3,4] As no systematic investigation on the influence of the 17α-substituent on the sign and value of the Cotton effect in pregnanes has been reported neither the value nor the sign of the Cotton effect of 17α-substituted pregnanes containing essentially different substituents at C-17 can be predicted. Consequently, the character of CD curves of pregnanes which have a sulphur function at position 17α cannot be postulated. Therefore in order to determine the configuration of compounds **1–5** we have used the formulated sector rule for episulphides[5,6] and the octant rule for thiolacetates.[7]

The episulphides sector rule determines the correlation between the sign of the Cotton effect and the chirality of the oxathiolane ring.[5,6]

Compounds **1–5** (Table 1) belong to the same series and contain a substituent at the 16α-position. Therefore if the configuration of the 17-centre in oxathiolanes **4** and **5** is known the configuration of this centre in compounds **1–3** can be determined. The chiralic-optical properties of the compounds **1–5** summarized in Table 1 were investigated both in the region of the carbonyl chromophore $n \to \pi^*$ transition of the 2O—C=O group and in the regions of the episulphide chromophore $n \to \sigma_5^*$ transition of oxathiolanes **4** and **5** and the carbonyl chromophore $n \to \pi^*$ transition of the thiolacetate group of thiolacetate **3**.

The configuration of the 17-centre in compounds **1–5** was based on the CD curves in the electronic absorption region of oxathiolanes **4** and **5**. Oxathiolanes in which the chromophore ring is fused to the steroid skeleton have an optically active transition near 250 mμ and it has been shown that the sign of the Cotton effect depends largely on the chirality of the chromophore ring.[5,6] Oxathiolanes **4** and **5** show a weakly positive Cotton effect centred near 255 mμ which may be attributed only to the episulphide chromophore $n \to \sigma_5^*$ transition.

Projections of two possible oxathiolanes epimeric at C-17 are shown in Fig 1 (the view along the bisectrix of the C—S—C angle and the view of the molecule from above projected on to the plane of episulfide ring). Projections of oxathiolanes **4B** and **5B** show that the rings B, C and D lie in the region of positive contribution. Consequently, positive contributions of the rings B, C and D must be subtracted from the large negative contribution of atom 16 (of chirality of the chromophore ring). Therefore for **4B** and **5B** a negative Cotton effect would be predicted by this rule. Dreiding models and projections (Fig 1) show that oxathiolanes **4A** and **5A** in which the oxathiolane ring is fused *cis* to the steroid skeleton have a flattened oxathiolane cycle with the chirality giving a positive contribution and positive contributions from A, B and C rings. This indicates that of two possible epimeric oxathiolanes **4** and **5** only epimers **4A** and **5A** with a 17β-acetoxy group can show a positive Cotton effect in the region of the episulphide chromophore $n \to \sigma_5^*$ transition. The above analysis completely excludes the structures **4B** and **5B** and testifies that the oxathiolanes **4** and **5** and consequently the whole series of compounds studied **1–3** belong to the pregnane and not to the isopregnane series.

In CD spectra of compounds **4–5** the Cotton effect observed near 222 mμ may be related to the $n \to \sigma_6^*$ transition. Theoretical consideration shows[6] that the signs of $n \to \sigma_5^*$ and $n \to \sigma_6^*$ transitions must be opposite. Coincidence of signs suggests a possible participation of the sulphur 3d orbital in the transition. Therefore, in our case this transition cannot be used to determine the configuration.

Table 1. CD spectra at + 25°

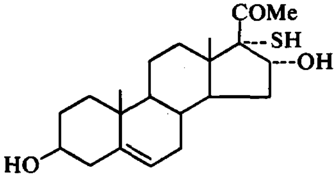
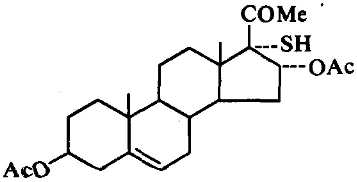
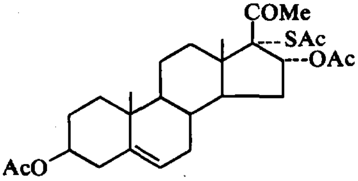
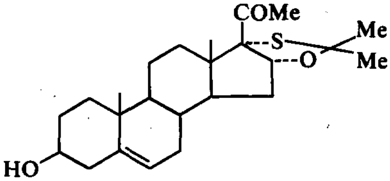
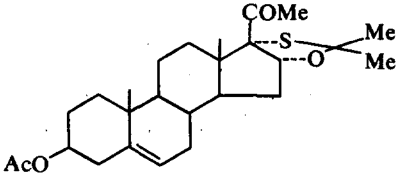
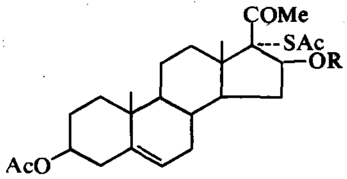
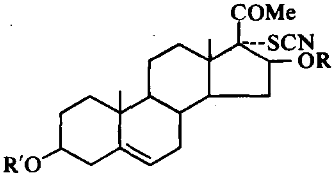
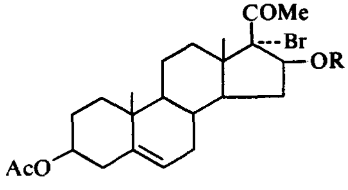
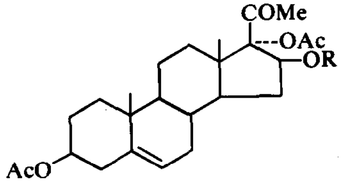
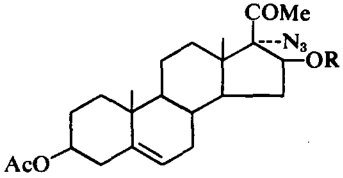
	Compound		dioxan		ethanol		hexane	
			λ max	Δε	λ max	Δε	λ max	Δε
1			299	−0·77				
2			296	−1·36	296	−2·67	300	−1·02
3			296	−1·30	296 256	−0·90 +0·5		
4			298	−5·56	300 255 222	−5·57 +0·56 +10·2		
5			298	−5·68	300 255 222	−6·10 +0·58 +10·2		
6		R=H	300 274	+0·26 −0·78	312 275	+0·17 −0·73	286	−0·57
		R=Ac	300	+3·96	300	+3·04	302	+4·30
7		R=R′=H	305	+3·74	314 278	+0·64 −0·54	330 300	0·034 −0·26
		R=R′=Ac	305	+5·63	303	+4·76	305	+6·34

Table 1. (*continued*)

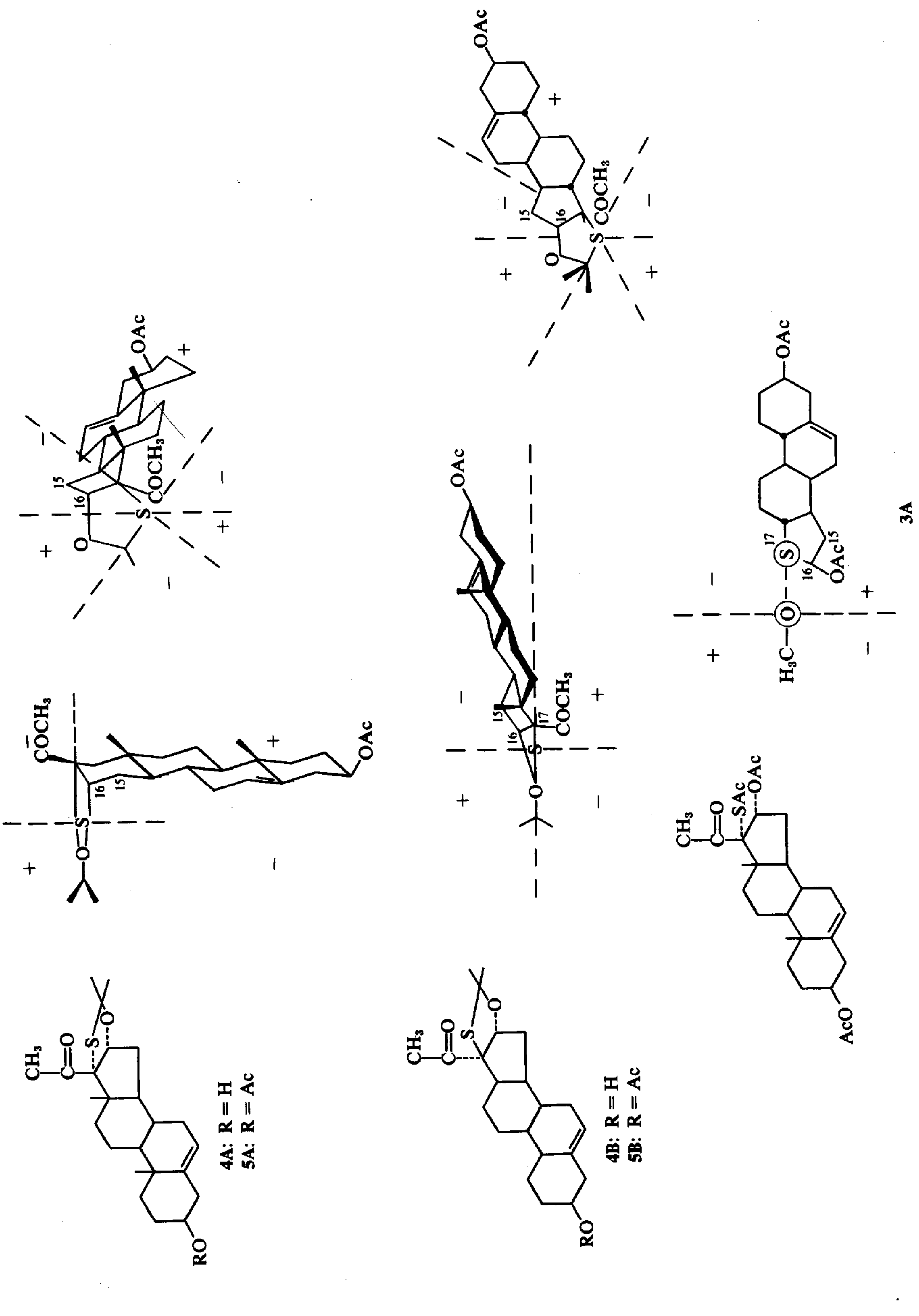
	Compound		dioxan		ethanol		hexane	
			λ max	Δε	λ max	Δε	λ max	Δε
8		R=H	308	+3·41	305	+4·30	300	−1·42
		R=Ac	308	+4·76	305	+4·40	308	+4·74
9		R=H	290	2·09	290	+1·71	250	+2·05
		R=Ac	286	−1·04	315	+0·17	288	−1·05
					275	−0·45		
10		R=H	310	+3·56	307	+3·00	309	+1·70
		R=Ac	308	+2·30	307	+2·30	309	+1·50

Investigation of CD curves of thiolacetate **3** in the region of thiolacetate $n \rightarrow \pi^*$ transition confirms the conformation of the 17-centre. Thiolacetates are an example of a chromophore with markedly restricted rotation and each primary conformation may be related to the magnitude and sign of the Cotton effect according to the octant rule.[7] The CD curve of thiolacetate **3** in ethanol has a positive Cotton effect in the region 256 mμ which we related it to carbonyl chromophore $n \rightarrow \pi^*$ transition of the thiolacetate group. Such a transition, not perceptible in the UV, has been demonstrated both in the ORD and CD spectra and appears near 270 mμ. A maximum displacement of Cotton effect for thiolacetate **3** is probably due to certain electronic interactions between the neighbouring polar groups.

Assuming the carbonyl σ bonds to be lying in the same plane as the bonds of the supposedly sp^2 hybridised sulphur we believe that only one preferable rotameric conformer (Fig 1) is possible for the 17α-thiolacetate group [provided there is a preferable conformation A (Fig 2) for the 17-acetyl group]. Octant projection (Fig 1) shows that in such a conformation the rings A and C lie almost symmetrically in relation to one of the planes of symmetry of the carbonyl chromophore of the thiolacetate group, but the rings B and D lie in the positive octant. Therefore, one would expect a positive Cotton effect for the 17α-thiolacetate **3**. The observed positive Cotton effect is in agreement with our prediction and with the configuration of substituents at the 17-centre, suggested for 17α-thiolacetate **3**.

It is evident from the analysis of CD curves of compounds **1–5** in the region of electronic adsorption of the 20—C=O group that the CD curves of the compounds discussed have been characterized by the negative Cotton effect.

It is known that 20-keto pregnanes have two preferred orientations of the 17β-acetyl side chain as illustrated in Fig 2 showing correspondingly positive and negative Cotton effects.[1,8] Pregnanes which do not carry substituents at C-16 and C-17 have a strongly positive Cotton effect that indicates the predominance of conformation A. It was concluded that introduction of an α-substituent at C-16 has very little or no influence on the Cotton effect.[1] Dreiding models and octant projection shows that in conformation A the 17α-substituent falls into a negative octant. In fact it is known that substitution of the 17α-H atom by halogen (Br, Cl, but not F[9]) results in an inversion of the Cotton effect.[3,4] 17α-Hydroxy and 17α-acetoxy groups do not cause a marked change of the Cotton effect and do not change the sign of the CD curve;[10,11] an 17α-azido group leaves the sign of Cotton effect unchanged.[12] We therefore conclude that the



4A: R = H
5A: R = Ac

4B: R = H
5B: R = Ac

3A

Fig. 1

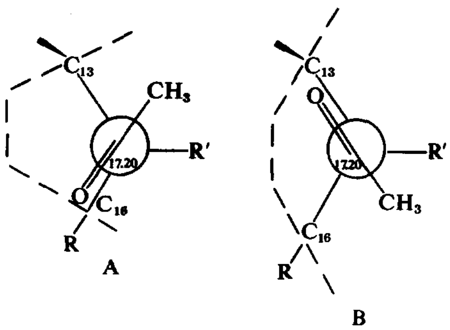


Fig 2.

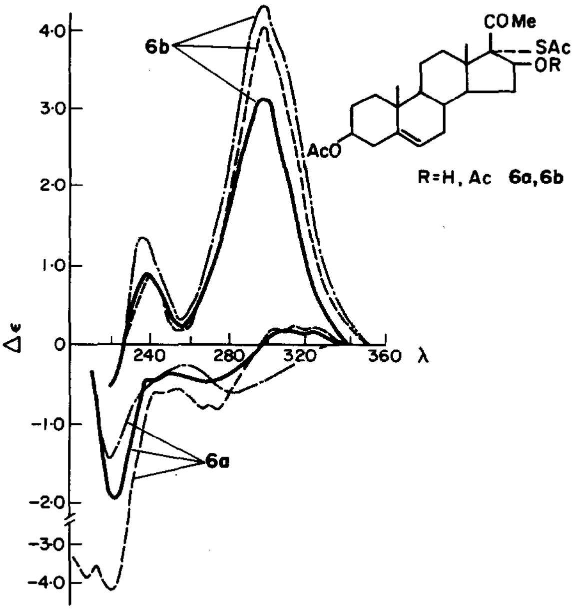


Fig 3. CD of 17α-thiolacetates **6a** and **6b** in hexane solution (-.-), in dioxan solution (---), in EtOH solution (—).

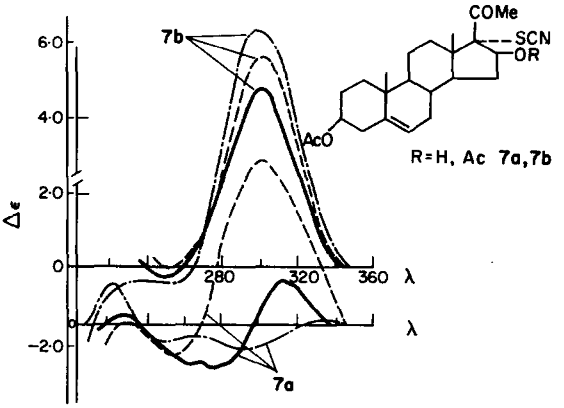


Fig 4. CD of 17α-thiocyanates **7a** and **7b** in hexane solution (-.-), in dioxan solution (---), in EtOH solution (—).

Cotton effect associated with the 20-keto chromophore is determined by the nature of the 17α-substituent.

It would be logical to assume that inversion of the Cotton effect by substituents (Cl, Br and S-containing) is explained by their negative contribution according to the octant rule in the positive Cotton effect of pregnenes in the preferred conformation A (Fig 2). In this case the retention of the sign of the Cotton effect by the —OH, —OAc, —F, —N_3 groups adjacent to the 20-keto chromophore may be explained either by these compounds existing in another conformation or by the fact that these substituents have very little or no influence[13] on the Cotton effect in the supposedly preferred conformation A. The latter seems to us to be more likely. To decide this point it was interesting to investigate by CD method the optical characteristics of 16β-hydroxypregnenes containing essentially different substituents at C-17. It is likely that intramolecular H-bonding between the 20—C=O and 16β-OH groups strongly favours conformation A for all compounds irrespective of the character of substituent at the position 17α. Therefore we investigated by the CD method the optical characteristics of 17α-R-substituted pregnen-3β,16β-diol-20-one **6a–10a** in different solvents. The results are summarised in Table 1 and the CD curves of these compounds are presented in Figs 3 and 4. The CD curve of **8a** in hexane in comparison with the curve of this compound in dioxan is characterized by a drastic decrease of amplitude of the carbonyl chromophore transition and by inversion of its sign. Such a drastic decrease of CD amplitude with the change of character of solvent observed earlier in 17α-bromopregnan-3β,16β-diol-20-one[14] is indicative of conformation mobility of the 17β-acetoxy group. As far as is known[15] this may result from the formation of intramolecular H-bonding in hexane between the 20-keto and 16β-OH groups which fall close together in *cis*-conformation. This leads to a preferred conformation A (Fig 2). Investigation of the IR spectra of all 16β-hydroxypregnenes (**6a–10a**) in CCl_4 shows that in the region of hydroxy absorption an intensive absorption band shifted to the lower-frequency region (3530–3460) due to the bonded peaks of hydroxy ketones.[16] It follows that conformation equilibrium A ⇄ B of 16β-hydroxypregnenes (**6a–10a**) in a non-polar solvent shifts to the left into conformation A where the 20—C=O and 16β-OH groups are involved in intramolecular H-bonding. As can be seen from the CD curves of 17α-thiolacetate **6a**, 17α-thiocyanate **7a** and 17α-bromo-derivative **8a** in hexane which are characterized by a negative Cotton effect, the curves differ in sign from the CD curves of 17α-acetate **9a** and 17α-azide **10a**. It should be noted that the character of CD curves of compounds **6a** and **7a** is indicative of great conformation mobility of the 17β-acetyl group (Figs 3 and 4).

Consequently it would be safe to say that according to the above agreement in 16α,17α-substituted pregnenes, the sign and value of the Cotton effect of 16β-hydroxyketones (**6a–10a**) in hexane is determined by the contribution of the substituent in the position 17α in the positive Cotton effect of the steroid's molecule in conformation A.

CD curves of 16β-hydroxyketones (**6a–8a**) in ethanol and dioxan compared with the curves obtained in hexane are characterized by the reversal of the sign of Cotton effect (Figs 3 and 4). The shape of the curves and the presence of two maxima in 17α-sulphur containing compounds (**6a** and **7a**) shows conformation mobility of the 17β-acetyl group. The CD amplitude of 17α-acetate **9a** is essentially unaffected in different solvents, but it is slightly less in ethanol than in hexane. 17α-Azide **10a** shows a definite increase in positive maximum in dioxan and ethanol compared with that in hexane. The observed increase of the amplitude with the growth of polarity of solvent in ketones **6a–8a** may be easily explained by conformational equilibrium of these compounds in conformations A ⇄ B shifted to the right due to some failure of intramolecular H-bonding in polar solvents[1,8,15] with due regard for the positive contribution of —SAc, —SCN, —Br-substituents in conformation B. Some decrease in the amplitude of the Cotton effect of 17α-acetate **9a** in ethanol compared with that in hexane may be explained also by the contribution of the conformation B to conformation equilibrium A ⇄ B, considering the above minor influence of the 17α-acetoxy group on the Cotton effect.

From this point of view it is difficult to explain the marked increase of the 17α-azide **10a** Cotton efffect with the change of the solvent. 17α-Azide **10a** seems to have preferred conformation A in all solvents studied (Fig 2).

16β-Acetoxy pregnenes (**6b–8b**) possessing —SCN, —SAc, —Br substituents at position 17α show in hexane, dioxan and ethanol an increase in the amplitude of the Cotton effect compared with the corresponding 16β-hydroxy compounds while 16β-acetoxy pregnenes (**9b–10b**) possessing —N_3 and —OAc groups at position 17α show a decrease of amplitude. The introduction of a *cis*-acetoxy function (16β-acetoxy group) into the vicinity of the 17β-acetyl group may be assumed to give rise to strong steric and polar interaction (which is definitely stronger than that in 16β-hydroxy compounds). Therefore the conformation equilibrium A ⇄ B of 16β-acetoxypregnenes can be expected to shift mainly to the right. From this assumption of preferred conformation B for 16β-acetoxypregnenes (**6b–10b**) it follows from the curves of these compounds given in Figs 3 and 4 that the 17α-SCN, 17α-Br, 17α-SAc groups, as we would expect, result in an inversion of the Cotton effect. But 17α-OAc group does not cause a marked change. A decrease in the maximum of the Cotton effect was observed for 17α-azide. Hence it follows that the azide group takes an intermediate position.

It is interesting to note that the observed different effects of the listed substituents are in direct relation to the length of the C17-R covalent bond (Table 2), namely: the substituents, having the length of C17-R bond ≥ 1·76 A° inverse the sign of Cotton effect whereas the substituents having the length of C17-R bond ≤ 1·49 A° do not cause a marked change. The observed relationship seems to have a general character for chromophore groups with a restricted rotation and, consequently, may be used for correlating the sign, the amplitude of the Cotton effect and the conformation of the compounds.

Table 2.

Bond	Interatomic distance, A°	Cotton effect of 16α,17α-substituted pregnenes
C—H	1·04	+
C—O	1·43	+
C—F	1·381	+
C—N	1·49	+
C—Br	1·937	−
C—S	1·815	−
C—Cl	1·767	−

EXPERIMENTAL

CD Spectra of the compounds **1–3** were recorded with a Roussel-Jouan Dichrograph (model I) with expanded scale at 25°. CD Spectra of the compounds **4–10** were determined on a recording Cary-60 spectropolarimeter with CD-6002 model attachment at 25°. The solvents used were EtOH, dioxan and hexane of spectroscopic purity grade. The concentrations were approximately 0·5 g/liter. The thickness of the optical path varied from 1 cm (at 320–250 mμ) to 0·05–0·01 cm (at 260–190 mμ). The instruments were calibrated using the analitically pure sample of the epiandrosteron ($\Delta\epsilon_{304} = +3{\cdot}294$).

The slit was programmed and spectral width was about 15 A° in the region 350–190 mμ.

Molecular ellipticity was estimated from the equation: $[\theta] = [\theta]_0 \cdot M/10l\,C$, where $[\theta]^0$ — the observed ellipticity, M — molecular weight, C — concentration in g/cm³, l — the length of optical path in cm. The value $\Delta\epsilon = \epsilon_L - \epsilon_R$ was determined from the relation $\Delta\epsilon = [\theta]/3300$.

No correction was taken on the refraction index. IR spectra of **6a–10a** were recorded by using a Perkin-Elmer spectrophotometer (model 257) in CCl_4 soln. The optical path was used 1 cm. Concentrations were in the order of 0·003 M. The instrument was calibrated on polystyrene film.

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