Communications to the Editor

[Chem. Pharm. Bull. 36(6)2274—2277(1988)]

CIRCULAR DICHROISM OF CYCLIC AMINO SUBSTITUTED Δ^4-3-KETOSTEROIDS

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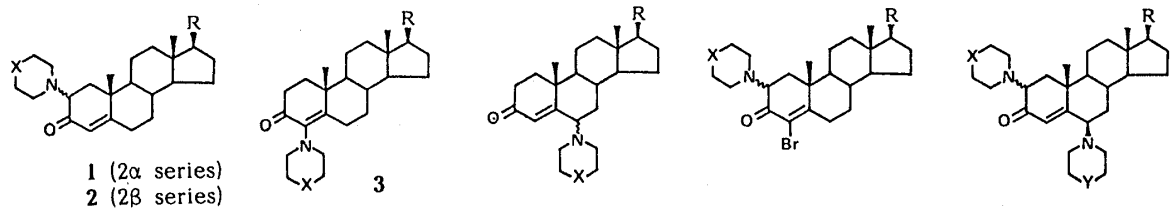
The circular dichroism (CD) of various steroidal α,β-unsaturated ketones having cyclic amino substituents near the enone system has been studied and the spectra provide significant information regarding the position and configuration of the substituents.

KEYWORDS — steroid; amino-steroid; CD; n-π* Cotton effect; π-π* Cotton effect; steroidal enone; α,β-unsaturated ketone

In α,β-unsaturated ketones, the signs of the Cotton effects associated with n-π* and π-π* transition reflect the chirality of the C=C-C=O chromophore[1] as well as the bulkiness and the electronic character of the substituents introduced in the axial α'-, γ-, and γ'-positions of the enone.[2] To our knowledge, however, there is no report concerning the spectral influence of amino substituents near the steroidal enone system.

Here, we report the CD spectra as the most effective method for the stereochemical assignment of the structure of cyclic amino steroidal enones. As examples, a number of cholest-4-en-3-oxo and 17β-acetoxyandrost-4-en-3-oxo derivatives having various cyclic amino functions (morpholino, piperazino,



1 (2α series)
2 (2β series)

3

R = OAc or C_8H_{17}
X,Y= O, NH, NAc, NCH_3, or NCH_2CH_2OH

4 (6α series)
5 (6β series)

6 (2α series)
7 (2β series)

8 (2α series)
9 (2β series)

N-methylpiperazino, and N-hydroxyethylpiperazino groups) at C_2, C_4, and C_6 positions, specifically, were synthesized from the corresponding 4-bromo- or 4,6β-dibromo-4-en-3-ones by displacement reaction with secondary cyclic amines.[3] Also, one of the most basic monoamino derivatives, 2α-morpholino-enone (1: R=OAc, X=O) and its 2β-isomer (2), were synthesized by the reductive debromination of the corresponding 2-morpholino-4-bromo-enones (6 and 7) with chromium(II) acetate[4] in DMSO under a CO_2 atmosphere.[5]

The CD spectra of the amino steroids were measured, these curves are characterized by two special features due to the C=C-C=O group: (i) a weak dichroic absorption in the region 310 - 330 nm (n-π* transition) and (ii) a strong band in the region 220 - 270 nm (π-π* transition). Since the amino-enone series, which has the same substituent configuration, gave analogous CD patterns, the observed phenomena in all runs will hereinafter be illustrated graphically by the typical representative curves of the morpholino derivatives (R=OAc, X=Y=O).[6]

At first, the CD spectra of the stereo- or the positional isomeric monoamino-enones, 2α-(1), 2β-(2), 4-(3), 6α-(4), and 6β-(5) derivatives, were compared with each other and with the spectra of unsubstituted

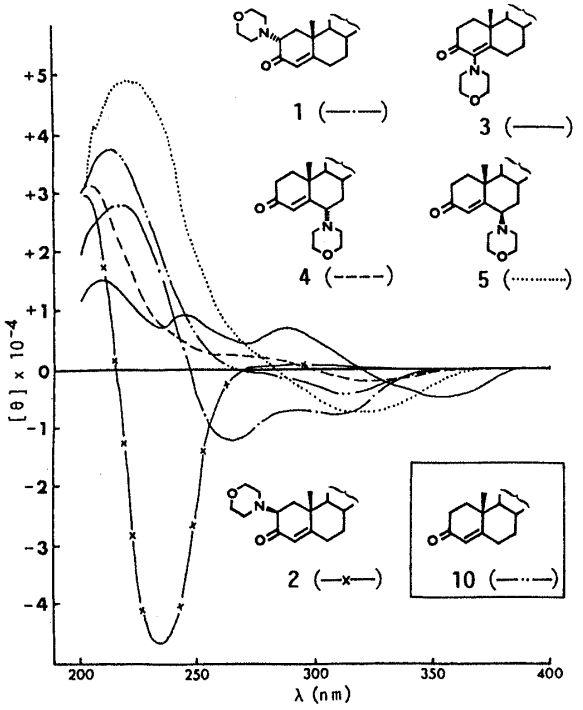


Fig. 1. CD Spectra of Testosterone Acetate **10** and Its Monomorpholino Derivatives (**1**, **2**, **3**, **4**, and **5**)

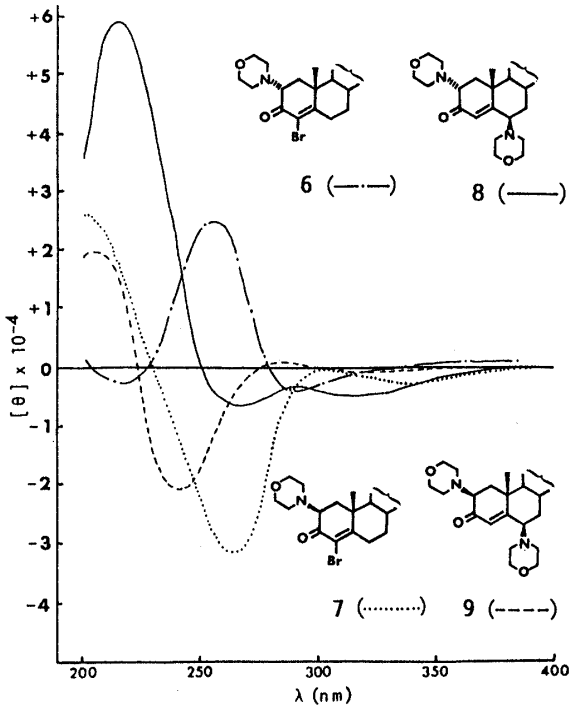
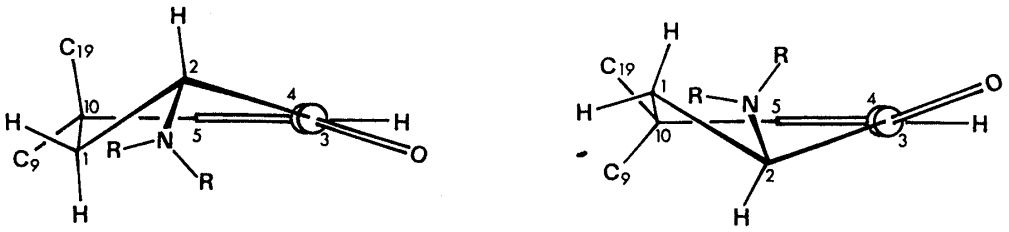


Fig. 2. CD Spectra of Disubstituted Testosterone Acetates (**6**, **7**, **8**, and **9**)

Δ^4-3-ketone 10 (testosterone acetate) (Fig. 1). The n-π^* transition above 310 nm gave a negative curve for all compounds with one exception (2), and among them, that of 3 occurred in a slightly longer wave length region (maximum at 357 nm). On the other hand, in the π-π^* transition region, 1, 3, 4, 5, and the parent enone 10 show positive Cotton effects.[7] The amplitude was higher in 5 and lower in 1, 3, and 4 than in 10, and 3 characteristically shows three positive maxima (285, 247, and 210 nm). In contrast, the 2β-amino-enone (2) characteristically exhibits a strong negative Cotton effect (maximum at 234 nm) in the region. Thus, these five isomers can easily be distinguished from each other by comparing their CD spectra.

Next the spectra of two pairs of disubstituted enones, 2α-amino-4-bromo-enone (6) and its 2β-isomer (7), and 2α,6β-diamino-enone (8) and its 2β-isomer (9), were compared with each other and with the corresponding monoamino-enones (Fig. 2). These disubstituted enones do show dramatic changes in their CD curves in the π-π^* transition region: the 2α-amino-4-bromo-enone (6) shows a positive and a negative maximum at 257 nm and 216 nm, respectively, whereas the 2β-isomer (7) exhibits a strong negative Cotton effect (maximum at 263 nm). Similarly, the 2α,6β-diamino compound 8 shows a strong positive Cotton effect at 215 nm, whereas the 2β-isomer (9) shows a distinct negative and a positive maximum at 240 nm and 205 nm, respectively.[8]

From these results, it became apparent that even in the disubstituted enone system, the CD spectra are most strongly affected by the reflection of the stereoisomeric amino functions at C_2. Furthermore, it appears that the significant difference on the curves between the 2α-amino enone system (1, 6, and 8) and their β-isomers (2, 7, and 9) in the π-π^* transition region may originate from the conformational difference of ring A caused by the bulky cyclic amino group at C_2. Namely, in the unsubstituted 10 and 2α-substituted enones (1, 6, 8), a normal half-chair form of the ring A with right-handed chirality may be the predominant conformation. On the other hand, in the 2β-substituted enones (2, 7, 9), an abnormal inverted half-chair conformation with left-handed chirality may be more favorable (Fig. 3).[9] So the former may have a positive and the latter may have an intense negative Cotton effect for the longer



right-handed chirality of 'normal half-chair' form [2α-R_2N-4-en-3-one]

left-handed chirality of 'inverted half-chair'form [2β-R_2N-4-en-3-one]

Fig. 3. The A-Ring of 2α- and 2β-R_2N-4-en-3-ones Projected Along the C_3-C_4 Bond, Showing the Basic Conformation

wavelength region of the π-π* transition, respectively.[1a)]

Thus, for assigning the isomeric structures of the cyclic amino substituted Δ^4-3-ketosteroids, the CD spectra can easily provide more definite information than other spectroscopy.

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5) On the reductive debromination with Zn-EtOH (50°C, 1 h) or Na_2SO_3-MeOH (25°C, 66 h), 2β-morpholino-4-bromo-enone (7) gave only 2α-morpholino-enone (1) isomerized at C_2 under the conditions (yield 75% and 14%, respectively). Furthermore, the treatment of 7 with Zn-HOAc (25°C, 15 h) caused reductive deamination to afford testosterone acetate (10: 30%) and its 4-bromide (64%). The compound 7 could successfully be converted into the desired 2β-morpholino-enone (2) only by the treatment with $Cr(OAc)_2$ in DMSO under a CO_2 atmosphere. The reaction was stopped in the course of the process (15 h) since a small amount of 2α-morpholino-4-bromo-enone (6), which may directly originate from the isomerization of 7, was detected by HPLC analysis at this time. Careful preparative TLC (CH_2Cl_2-MeOH(19:1)) of the resulting mixture provided the 2β-morpholino derivative 2 (yield 15%, Rf 0.23), 6 (trace), and 7 (recovered 72%). On the other hand, the more stable 2α-morpholino compound 1 was easily obtained by the reductive debromination of 6 with $Cr(OAc)_2$ in DMSO (25°C, 80 h) in good yield (87%). The physicochemical data are the following.

1: colorless needles; mp 179-180°C(dec.) from ether; IR ν_{max}cm^{-1} (CCl_4): 1737, 1680, 1624, 1247; UV λ_{max}nm (ethanol): 238 (ε=14000); ^{1}H-NMR ($CDCl_3$/TMSint) δ: 0.84, 1.25, 2.05 (3H each, s), 2.75 (4H, t, J=7.3Hz), 3.40 (1H, dd, $J_{2\beta,1\alpha}$=13.6Hz, $J_{2\beta,1\beta}$=4.6Hz), 3.75 (4H, t, J=7.3Hz), 4.59 (1H, t, J=7.3Hz), 5.67 (1H, s) ppm; MS m/z: 415 (M^+), 413, 398, 330 (M^+-C_4H_7NO), 315, 218, 86 ($C_4H_8NO^+$).

2: colorless needles; mp 168-170°C from ether; IR ν_{max}cm^{-1} (CCl_4): 1736, 1676, 1625, 1245; UV λ_{max}nm (ethanol): 242 (ε=14000); ^{1}H-NMR ($CDCl_3$/TMSint) δ: 0.83, 1.27, 2.04 (3H each, s), 2.60 (4H, m), 3.12 (1H, dd, $J_{2\alpha,1\alpha}$=4.6Hz, $J_{2\alpha,1\beta}$=10.5Hz), 3.72 (4H, t, J=7.3Hz), 4.60 (1H, t, J=7.3Hz), 5.71 (1H, s) ppm; MS m/z: 415 (M^+), 413, 398, 330 (M^+-C_4H_7NO), 315, 218, 86 ($C_4H_7NO^+$).

6) All CD spectra were obtained on a JASCO-J20 automatic recording spectropolarimeter. Scan rates and sensitivities were selected to give an optimum signal-to-noise ratio. The CD data for the morpholino derivatives represented in Figs. 1 and 2 are as follows: CD (c=0.10, methanol) $[\theta]^{25}$(nm), i: inflection):

1: -8600 (312)(negative max.), -13950 (263)(negative max.), 0 (248), +28200 (218)(positive max.), +18300 (200).

2: +830 (310), 0 (270), -47300 (234)(negative max.), 0 (215), +31540 (200).

3: -5800 (357)(negative max.), 0 (318), +4650 (288)(positive max.), +8650 (245)(positive max.), +15500 (208) (positive max.).

4: -2080 (320)(negative max.), 0 (296), +11700 (225)(i), +31250 (202)(positive max.).

5: -7500 (317)(negative max.), 0 (284), +18750 (250)(i), +49600 (218)(positive max.).

6: +1730 (373)(positive max.), 0 (325), -4700 (286)(negative max.), 0 (278), +25300 (257)(positive max.), 0 (229), -3500 (216), 0 (205), +2500 (200).

7: -2230 (338)(negative max.), 0 (300), -31500 (263)(negative max.), 0 (231), +26500 (202)(positive max.).

8: -4990 (320)(negative max.), -2770 (285), -6100 (263)(negative max.), 0 (251), +62000 (215)(positive max.).

9: -550 (320)(negative max.), 0 (296), 0 (277), -21100 (240)(negative max.), 0 (223), +19400 (205)(positive max).

10: -4620 (310)(negative max.), -1150 (280)(i), 0 (264), +17300 (235)(i), +38100 (212)(positive max.).

Since the similar curves were obtained for the other compounds (3a-h, 5a-g, 6a-c, 7a-g, 8a-l, and 9a-d), the only positive and negative maxima are listed below:

3a (R=OAc, X=NH): -5800(350), +4800(286), +7530i(240), +23200(205); 3b (R=OAc, X=NAc): -5100(350), +4200(288), +8670(249), +23400(215); 3c (R=OAc, X=NCH_3): -6500(349), +4160(285), +11100(244), +19500 (203); 3d (R=OAc, X=NCH_2CH_2OH): -6060(354), +5870(287), +8070(244), +22100(204); 3e (R=C_8H_{17}, X=O): -6900(353), +5350(292), +6000i(248), +22600(206); 3f (R=C_8H_{17}, X=NAc): -6300(350), +4900(291), +10700 (242), +24800(201); 3g (R=C_8H_{17}, X=NCH_3): -6300(355), +6300(293), +7300(247), +24300(204); 3h (R=C_8H_{17}, X=NCH_2CH_2OH): -5600(355), +6700(293), +8600i(247), +23800(204).

5a (R=OAc, X=NH): -4930(312), +48300(220); 5b (R=OAc, X=NAc): -4800(317), +41700(225); 5c (R=OAc, X=NCH_3): -5150(320), +33400(223); 5d (R=OAc, X=NCH_2CH_2OH): -6800(318), +44500(224); 5e (R=C_8H_{17}, X=O): -5700(317), +43600(216); 5f (R=C_8H_{17}, X=NAc): -4700(318), +38300(219); 5g (R=C_8H_{17}, X=NCH_3): -5100(316), +36400(217);

6a (R=OAc, X=NAc): +1710(377), -5040(287), +20500(263); 6b (R=OAc, X=NCH_3): +1810(378), -4600(290), +19400(258); 6c (R=C_8H_{17}, X=O): +1500(372), -5100(292), +24300(257).

7a (R=OAc, X=NAc): -2300(339), -36100(278), +28200(215); 7b (R=OAc, X=NCH_3): -1900(335), -33700(265), +21300(208); 7c (R=OAc, X=NCH_2CH_2OH): -1600(334), -30100(270), +22200(204); 7d (R=C_8H_{17}, X=O): -2000(337), -34200(263), +25500(208); 7e (R=C_8H_{17}, X=NAc): -2200(335), -31100(267), +23100(208); 7f (R=C_8H_{17}, X=NCH_3): -1960(330), -31700(264), +24100(208); 7g (R=C_8H_{17}, X=NCH_2CH_2OH): -1830(335), -36100 (268), +21700(208).

8a (R=OAc, X=Y=NAc): -3600(320), +54300(221); 8b (R=OAc, X=Y=NCH_3): -3480(311), +46800(215); 8c (R=OAc, X=Y=NCH_2CH_2OH): -4990(318), +52000(218); 8d (R=C_8H_{17}, X=Y=O): -4900(320), +60100(215); 8e (R=C_8H_{17}, X=Y=NAc): -3300(320), +42200(219); 8f (R=C_8H_{17}, X=Y=NCH_3): -4500(315), +45400(216); 8g (R=C_8H_{17}, X=Y=NCH_2CH_2OH): -5800(310), +52600(214); 8h (R=OAc, X=O, Y=NCH_3): -5200(325), +59500(224); 8i (R=OAc, X=O, Y=NCH_2CH_2OH): -4860(312), +49800(217); 8j (R=OAc, X=NCH_3, Y=O): -5300(323), +51300(220); 8k (R=OAc, X=NCH_2CH_2OH, Y=O): -5490(328), +57900(225); 8l (R=C_8H_{17}, X=O, Y=NCH_3): -4600(315), +46500(219).

9a (R=C_8H_{17}, X=Y=O): -500(315), -22100(240), +19900(205); 9b (R=C_8H_{17}, X=Y=NAc): -300(315), -46100 (248), +22500(218); 9c (R=C_8H_{17}, X=Y=NCH_3): -250(313), -47900(240), +28700(215); 9d (R=C_8H_{17}, X=O, Y=NCH_3): -310(312), -43100(245), -23100(213).

7) Of considerable interest is the fact that 6β-amino compound 5 exhibits a normal positive π-π* Cotton effect, demonstrating that there is no electronic interaction between the lone pair of the 6β-hetero atom and the Δ^4-3-keto electrons in 5, as observed in 6β-hydroxy or 6β-acetoxy compounds.[2a] It is highly plausible that such electronic interaction may be disturbed by hindered rotation of the bulky cyclic alkyl group bonded to the nitrogen atom, which may interact with the enone system.

8) In 2α-amino compounds 1, 6, and 8, negative CD bands (263, 286, and 263 nm, respectively) were also observed but the origin of the bands is not defined.

9) When C_2 bears a bulky axial substituent, steric interference may occur between this substituent and the 10-methyl group, and this interference may be relieved by a conformational change of ring A. Thus, a 2β-substituent should favor the inverted half-chair conformation for ring A, while a 2α-substitution should stabilize the normal half-chair conformation (see reference 1e).

(Received March 7, 1988)