Proc. Indian Acad. Sci. (Chem. Sci.), Vol. 90, Number 4, August 1981, pp. 281–290.

A total synthesis of 4-cyano-1,3-dimethoxy-2-azaestra-1,3,5(10)-trien-17β-ol and its configuration assignment

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MS received 11 March 1981; revised 9 May 1981

Abstract. A total synthesis of 4-cyano-1,3-dimethoxy-2-azaestra-1,3,5(10)-trien-17β-ol (6a) has been achieved starting from 4-cyano-1,3-dimethoxy-5,6,7,8-tetrahydroisoquinoline (1a). Dichromate oxidation of 1a gave the 8-oxo derivative (1c) whose structure was confirmed unambiguously by the lanthanide induced chemical shift method. Grignard reaction of 1c with vinyl magnesium bromide followed by condensation of the vinyl-alcohol with 2-methyl-cyclopentane-1,3-dione resulted in the seco-dione (2) in 50% yield, which was cyclised with *p*-toluene sulfonic acid to the pentaenone (3a). Sodium borohydride reduction of 3a, stereoselective partial hydrogenation of the 14,15-double bond in 3b followed by isomerisation of the 8,9-double bond in 4 to 9,11-position and catalytic reduction of the 9,11-double bond gave the title compound (6a). The 14α,8β,9α-configuration in 6 was tentatively assigned on the basis of its NMR spectrum. The CMR spectra of the steroidal derivative and also the tetrahydroisoquinoline derivative (1b) have been studied and the configuration assigned to the steroid has also been supported by this study.

Keywords. Steroids; azasteroids; seco-dione; 5,6,7,8-tetrahydroisoquinoline; ^{13}C NMR.

1. Introduction

The structure elucidation and configuration assignment of steroid hormones, and the recognition of their physiological properties have led to an explosive increase in the synthesis of a variety of steroid molecules in the hope of getting compounds with enhanced or advantageously modified medicinal properties. One of the most important modifications of steroids has been the introduction of hetero atoms like nitrogen, oxygen and sulphur into the perhydrocyclopentanophenanthrene nucleus (Huisman 1973). Azasteroids have received maximum attention among the heterocyclic steroids probably because of interesting physiological properties reported for such compounds (Alauddin and Martin-Smith 1962). Our earlier efforts to synthesise 4-cyano-1-methyl-3-ethoxy-2-azaestra-1,3,5(10)-trien-17β-ol were unsuccessful and resulted in the formation or 2-azaequilenin derivative (Kasturi 1976). In view of the very few reports on the total synthesis of 2-azasteroids

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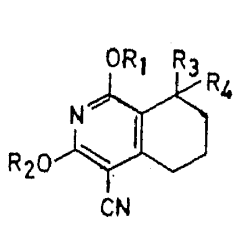
(Charat *et al* 1978) and also of the unique biological properties these compounds are known to possess, we continued our earlier work in this area and now report a stereospecific total synthesis of 4-cyano-1,3-dimethoxy-2-azaestra-1, 3,5 (10)-trien-17β-ol (6a, figure 1).

2. Results and discussion

The scheme adopted for the synthesis of the steroid skeleton is based on the $AB + D \rightarrow ABD \rightarrow ABCD$ approach. The azatetralone (1c) forms the *AB* part



1

a, R_1 = Me ; $R_2 = R_3 = R_4$ = H

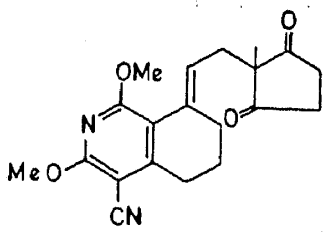
b, $R_1 = R_2$ = Me ; $R_3 = R_4$ = H

c, $R_1 = R_2$ = Me ; $R_3 + R_4$ = O

d, $R_1 = R_2$ = Me ; R_3 = CH=CH_2 ; R_4 = OH

e, R_1 = Et ; $R_2 = R_3 = R_4$ = H

f, R_1 = Et ; R_2 = Me ; $R_3 = R_4$ = H



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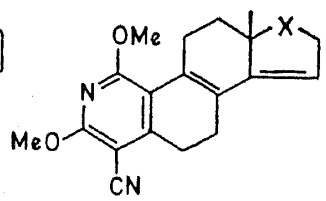
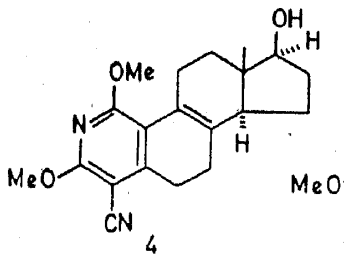


3

a, X = C=O

b, X = C(OH)H



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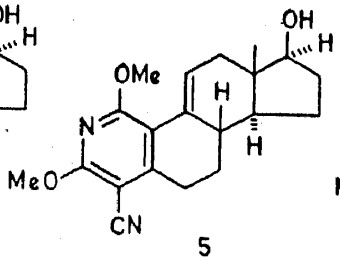

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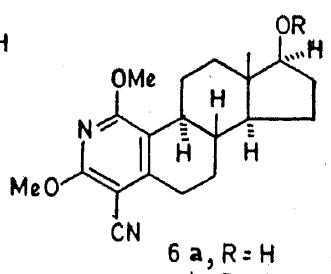
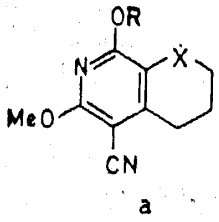
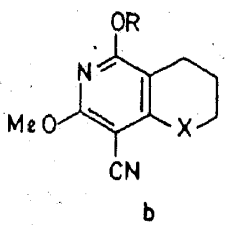


6 a, R = H

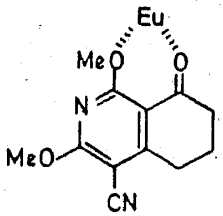
b, R = Ac

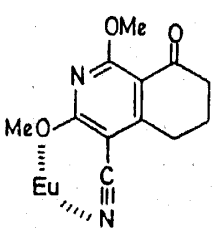


a



b





7 a, R = Et ; X = C=O

7 b, R = Et ; X = C=O

8 a, R = Et ; X = CHOH

8 b, R = Et ; X = CHOH

9 a, R = Me ; X = CHOH

Figure 1.

and is the key intermediate in the projected total synthesis. The first stage of the synthesis, thus consisted of the preparation of 1c. Kasturi *et al* (1973), and Van der Baan and Bickelhaupt (1974) independently reported the formation of 4-cyano-3-hydroxy-1-methoxy-5,6,7,8-tetrahydroisoquinoline (1a) in high yields during the Knovenagel condensation of 2-carbomethoxycyclohexanone and malononitrile. Compound (1a) was thus chosen as the starting material for the synthesis of 6a. Methylation of 1a gave the dimethoxy compound (1b) in 90% yield. This was then subjected to benzylic oxidation using sodium dichromate-sulphuric acid mixture. Chromatography of the neutral portion of the crude oxidation product yielded a colourless ketone (1680 cm^{-1}, conjugated carbonyl, M^+ 232). As Sugimoto *et al* (1956) have reported that benzylic oxidation of 5,6,7,8-tetrahydroisoquinoline leads to a mixture of 5- and 8-oxo compounds, it became necessary to unambiguously assign the position of the keto group in the oxidation product for which purpose the lanthanide induced chemical shift method was used employing $Eu(dpm)_3$ as the shift reagent. The structurally similar compounds 7 and 8 were similarly synthesised for a comparative study.

The spectra were recorded by an incremental addition of the substrate to the lanthanide shift reagent (LSR) in solution. Table 1 shows the shifts observed for the relevant protons in each compound. Two types of complexes with the Eu ion are possible as shown in figure 1. In each of the compounds under study, oxygen is a harder base than nitrogen and so coordination *via* oxygen is expected to be much stronger. In compounds 7 and 8, the magnitude of the shifts of the $-OCH_2$ protons are much greater than that of the $-OCH_3$ protons as indicated in table 1 by the shift ratios, showing that the $-OCH_2$ protons are in close

Table 1. Lanthanide induced chemical shifts of compounds 7 to 10

Structure	L/S	Induced shifts (Hz)		Shift ratio
		$-OCH_3$	$-OCH_3$	$-OCH_2/-OCH_3$
	0·2	24	54	2·2
7	0·4	30	78	2·6
	0·6	42	114	2·7
		$-OCH_3$	$-OCH_3$	$-OCH_2/-OCH_3$
	0·2	28	46	1·64
8	0·4	40	64	1·60
	0·6	58	100	1·72
		$-OCH_3$ (1)	$-OCH_3$ (3)	
	0·2	5·4	2·2	2·45
9	0·4	13·8	4·6	3·00
	0·6	111·6	36·4	3·08
		$-OCH_3$ (3)	$-OCH_3$ (1)	$-OCH_3$ (1)/$-OCH_3$ (3)
	0·2	2·2	3·96	1·8
10	0·4	2·58	6·18	2·4
	0·6	34·2	85·8	2·5

proximity to the hydroxyl group in 8 and the keto group in 7 to which the Eu ion complexes. This large shift ratio can be explained only if the keto group were at C–8 and not at C–5. The alcohol (9a) and the ketone (1c) are structurally similar to the compounds (7) and (8) respectively. From the data in table 1, it is seen that the shifts induced in one of the methoxy protons in the alcohol (9) and the ketone (1c) are much larger than the other. By analogy with the compounds (7) and (8), it should be the methoxy protons at C–1. This behaviour could be explained only if the keto group were at C–8 and not at C–5. The structure of the ketone (1c) was thus established firmly beyond doubt.

Grignard reaction of 1c with excess vinyl magnesium bromide in THF at −60–80° C gave the vinyl carbinol (1d), [IR: 3580 (OH stretch) and 2240 (C≡N) cm^{-1}] purified by column chromatography and TLC. The NMR spectrum exhibiting the characteristic *AB* splitting pattern (12 lines) between 4·77–6·1δ confirmed the presence of vinyl alcohol and the structure 1d. The vinyl alcohol (1d) was condensed with 2-methylcyclopentane-1,3-dione in refluxing xylene with molar amounts of methyl amine to give the seco-dione (_) in 50% yield. Cyclisation of 2 to the pentaenone (3a) was rather sluggish. It was, however, achieved by refluxing the seco-dione (2) in a mixture of xylene-dioxane with excess *p*-tosic acid.

Reduction of 3a with sodium borohydride in methanol gave the 17β-alcohol (3b). The 17β-configuration was assigned to the hydroxyl group in analogy with the products obtained by the sodium borohydride reduction of similar pentaenones (Burckhalter and Scivolino 1967). Moreover, the 17α-H triplet in the NMR spectrum of 3b (δ 3·9, $J = 9$Hz) was comparable to that of the 17α-H triplet of testosterone (Bhacca and Williams 1964). The Δ^{14}-double bond in 3b was reduced stereoselectively over 5% $Pd/CaCO_3$ catalyst and the product obtained was a single tetraenol isomer (NMR: δ 0·81, *s*, 3H, 18–Me). The absence of any vinylic proton signal in the NMR spectrum confirmed that the Δ^{14}-double bond had been reduced. The occurrence of the 18-methyl signal at δ0·81 led to the assignment of the 14α-configuration to the tetraenol (4). Tetraenols with the 14β-configuration exhibit the 18-methyl signal at a comparatively lower field (Bhacca and Williams 1964).

The crucial step in the total synthesis of estradiol-3-methyl ether analogue (6a) is the trans-reduction or the 8,9-double bond. Birch reduction failed to yield the required product since the heteroaromatic nucleus was labile to it (Charat *et al* 1978). The 8,9-double bond in 4 was hence isomerised to the 9(11)-position by refluxing with methanolic hydrochloric acid for 16 hr. The occurrence of an olefinic proton signal at δ 6·9 (br, 1H, 11-H) in the NMR spectrum of 5 confirmed the presence of Δ^{9} (11)-double bond. Catalytic hydrogenation of 5 over 10% palladium on charcoal gave a single isomer. In analogy with earlier work (Burckhalter and Scivolino 1967) on the catalytic reduction of similar estratetraenols, the 8β,9α-stereochemistry was tentatively assigned to 6a. A total synthesis of 4-cyano-1,3-dimethoxy-2-azaestra-1,3,5 (10)-trien-17β-ol (6a) was thus completed.

A study of the ^{13}C NMR spectrum of the 17β-acetate derivative of 6a lent further support to the configuration assigned. The basic unit of the steroid (6) is the 4-cyano-1,3-dimethoxy-5,6,7,8-tetrahydroisoquinoline (1b). Hence, the ^{13}C NMR spectrum of 1b was examined first. The noise-decoupled spectrum showed

the presence of 10 well-resolved signals with two of them (δ_c 53·97 and 22·13*) more intense indicating signal overlap. The signal at δ_c 53·97 (*q*, off-resonance decoupled spectrum (ORDS)) was readily assigned to two methoxy carbons. The six lines in the δ_c 80–165 range remained as singlets in the ORDS and could be assigned to the five aromatic carbons and the nitrile carbon. Hetero aromatic ring chemical shifts are calculated according to equation (1) (Rectofsky and Friedel 1968):

$$\delta_c\ (k) = C + \sum_i A_{ik}\ (R_i) \qquad (1)$$

where C_k is the constant term for nucleus k (Chemical shift of carbon k in pyridine in this case) and A_{ik} is the shift increment predicted for carbon k upon introduction of substituent R_i at carbon (i). Using the above equation for monosubstituted pyridines, the substituent shifts for methoxy and cyano groups were obtained. Applying the principle of additivity of substituent shifts for such systems (Stothers 1972), the specific assignments for the five aromatic carbons were made. The remaining signal at δ_c 112·5 was assigned to the nitrile carbon. The signals due to the methylene carbons in 1**b** could not be assigned specifically. The completely decoupled spectrum of 4-cyano-1,3-dimethoxy-2-azaestra-1,3,5 (10) trien-17β-yl acetate (6**b**) was examined next. The spectrum showed 21 lines. The intensity of the signal at δ_c 58·5 indicated overlap due to two carbons thus accounting for all carbon atoms in the molecule. The signals at δ_c 171·1 (*s*, ORDS), 58·5 (*q*, 2C), 113·6 (*s*), 21·0 (*q*) and 12·9 (*q*) were readily assigned to the acetyl carbonyl, the two methoxy carbons, the nitrile carbon, the acetyl methyl carbon and the 18-Me carbon based on their chemical shift values. The aromatic carbon (C-1, C-3, C-4, C-5, and C-10) chemical shifts were obtained by the principle of additivity of substituent effects obtained from the model compound (1**b**) described earlier. From a study of the ^{13}C spectra of a variety of estranes reported in literature (Blunt and Stothers 1977), it was found that the chemical shift of C-17 in 17β-acetates is invariably deshielded (δ_c 82–83) compared to the C-17 in 17α-acetates (δ_c 81–82). The signal at δ_c 82·7 (**d**) evidently due to a methine carbon was assigned to C-17 confirming indirectly the β-configuration of the acetate moiety. The assignment of the other carbons were made by using the technique of off-resonance decoupling and by comparison with the spectra of known estranes and will not be discussed in detail here. The signal at δ_c 49·7 (*d*) was assigned to C-14 and tallied well with those of other estrane derivatives with the 14α-configuration. The C-14 signal in estrane derivatives with 14β-configuration is invariably shielded (δ_c 44–46). Configuration at C-8 and C-9 could not be assigned specifically due to their close chemical shift values. Table 2 summarises the CMR shifts of all the carbons in the acetate derivative of 6**a**. Taking into account the presence of the hetero atoms and the various substituents, the assigned carbon chemical shifts compare very well with those of natural, estratrien-17β-acetate and 3-methoxyestratrien-17β-acetate and hence, lend support to the configuration assignment based on its PMR spectra and other chemical analogies.

The biological properties of these molecules are currently being evaluated.

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* All chemical shifts are represented in δ_c values w.r.t. TMS = 0.

Table 2. ^{13}C shielding data for 4-cyano-1,3-dimethoxy-2-azaestra-1,3,5 (10)-17β-yl acetate (6b).

Peak No.	Chemical shift	Nature of signal (ORDS)	C-atom
1.	170·1	*s*	$-\underline{C}O-CH_3$
2.	167·6	*s*	C–1 or C–3
3.	164·8	*s*	C–3 or C–1
4.	154·8	*s*	C–5
5.	114·0	*s*	C–10
6.	113·6	*s*	$C\equiv N$
7.	89·2	*s*	C–4
8.	82·7	*d*	C–17
9.	58·5	*q*	$(-O\underline{C}H_3)_2$
10.	49·7	*d*	C–14
11.	43·1	*s*	C–13
12.	38·2	*d*	C–8 or C–9
13.	37·1	*d*	C–9 or C–8
14.	30·0	*t*	C–16
15.	27·7	*t*	C–6
16.	25·6	*t*	C–7 or C–11
17.	24·9	*t*	C–11 or C–7
18.	23·4	*t*	C–15
19.	37·5	*t*	C–12
20.	21·0	*q*	$-CO\underline{C}H_3$
21.	12·9	*q*	C–18

3. Experimental

All m.ps. and b.ps. reported herein are uncorrected. The UV spectra were recorded in 95% ethanol on a Unicam Sp 700 A spectrophotometer and the IR on a Perkin-Elmer model 700 spectrophotometer. The PMR spectra were recorded on a Varian T-60 or a HA-100 D spectrometers. The ^{13}C NMR spectra were recorded on a Brucker WH 270 MHz instrument at 67·89 MHz in the pulsed mode. Chemical shifts are quoted relative to TMS ($\sigma = 0$ ppm) as internal standard. All organic extracts were dried over anhydrous sodium sulphate before solvent removal. Microanalyses were carried out by Messrs Thyagarajan and Ramaprasad of our Department.

3.1. *Alkylation of the pyridinols* (1a *and* 1e)

A mixture of the pyridinol (1a, 20·4 g) silver oxide (11·6 g) and methyl iodide (28 ml) in benzene (75 ml) was refluxed with stirring for 8 hr. The cooled reaction mixture was filtered and the residue washed with benzene. The benzene solution was washed with an ice-cold 10% NaOH solution (3 × 4·0 ml). The alkali washings were extracted with an additional portion of benzene. The combined benzene solution was washed with water. Solvent removal gave a crude

residue (19·6 g) which was crystallised from hexane to give 4-cyano-1,3-dimethoxy-5,6,7,8-tetrahydroisoquinoline (1b), m.p. 82–84°; NMR ($CDCl_3$): 1·6–2 (*m*, 4H), 2·3–3 (*m*, 4H) and 4·0 [*s*, $(OCH_3)_2$, 6H] (Found: C, 66·04; H, 6·43; N, 12·85. $C_{12}H_{14}N_2O_2$ requires: C, 66·18; H, 6·72; N, 12·80%).

Similarly, methylation of 1e (2·18 g) with silver oxide (1·16 g) and methyl iodide (2·8 ml) in benzene (15 ml) followed by recrystallisation from benzene-hexane yielded 4-cyano-1-ethoxy-3-methoxy-5,6,7,8-tetrahydroisoquinoline (1f, 2g), m.p. 70–72°; NMR (CCl_4): 1·4 (*t*, J = 7Hz, $-O-CH_2-CH_3$, 3H), 1·6-1·9 (*m*, 4H), 2·4–3 (*m*, 4H), 4·0 (*s*, OCH_3, 3H) and 4·4 (*q*, J = 7Hz, $-O-CH_2-CH_3$, 2H) Found: C, 66·91; H, 7·21; N, 11·91, $C_{13}H_{16}N_2O_2$ requires: C, 67·23; H, 6·9; N, 12·07%).

3.2. *Oxidation of 1b and 1f*

To a stirred mixture of the azatetralin (1b, 10·9 g) in conc. H_2SO_4 (9 ml) and glacial acetic acid (123 ml) was added sodium dichromate (25 g) slowly with stirring so that the temperature did not rise above 80°. The addition was done over a period of 1 hr and the heterogeneous reaction mixture was stirred at room temperature for 10 hr. It was diluted with 1·5 litres of water and extracted with benzene (4 × 200 ml). The combined benzene extracts were washed successively with water (3 × 100 ml), 10% sodium bicarbonate solution (4 × 100 ml) and water (3 × 100 ml). The benzene layer was dried. Solvent removal *in vacuo* gave a crude product (9·2 g) which was chromatographed over a column of neutral alumina (250 g). Elution with benzene gave the starting azatetralin (1b, 2·2 g). Further elution with benzene-chloroform (3:1) afforded 4-cyano-1,3-dimethoxy-8-oxo-5,6,7,8-tetrahydroisoquinoline (1c) as colourless solid (7·54 g) which could be recrystallised from benzene-hexane, m.p. 168–170°, IR (nujol): ν_{max} 1680 (C=O) and 2240 cm^{-1} (C≡N); NMR (CCl_4): 1·83–2·6 (*m*, 4H, CH_2 protons), 2·83–3·1 (*m*, 2H), 4·0 and 4·07 [2*s*, $(-OCH_3)_2$, 6H]; (Found: C, 62·21; H, 5·20; N, 12·03. $C_{12}H_{12}N_2O_3$ requires: C, 62·07; H, 5·16; N, 12·07%).

Similarly, oxidation of 1f (2·32 g) with sodium dichromate gave the crude oxidation product (2·2 g) which was chromatographed over neutral alumina (70 g). The benzene-chloroform (3:1) eluent gave the required ketone, 4-cyano-1-ethoxy-3-methoxy-8-oxo-5,6,7,8-tetrahydroisoquinoline (7a, 1·6 g), m.p. 121–122° (benzene-hexane); IR (nujol): ν_{max} 2240 (C≡N) and 1680 cm^{-1} (C=O); NMR ($CDCl_3$): 1·5 (*t*, J = 7 Hz, $-OCH_2CH_3$, 3H), 2–2·3 (*m*, 2H), 2·4–2·8 (*m*, 2H), 3–3·3 (*m*, 2H), 4·05 (*s*, $-OCH_3$, 3H) and 4·6 (*q*, J = 7Hz, $-OCH_2CH_3$, 2H) (Found: C, 63·21; H, 5·99; N, 11·05. $C_{13}H_{14}N_2O_3$ requires: C, 63·42; H, 5·69; N, 11·38%).

3.3. *Reduction of the ketones (1c) and (7a) with sodium borohydride (SBH)*

To a stirred solution of the ketone (1c, 1g) in methanol was added SBH in small portions. The stirring was continued at room temperature for 3 hr after which the reaction was quenched by the addition of excess acetone. The solvent was removed *in vacuo* and water added to the residue. The resulting solid was filtered, dried and recrystallised from benzene to give 4-cyano-1,3-dimethoxy-8-

hydroxy-5,6,7,8-tetrahydroisoquinoline (9a, 900 mg, m.p. 98–100° C); IR (nujol): ν_{max} 3400–3020 (*b*, OH) and 2220 cm^{-1} (C≡N); NMR ($CDCl_3$): 1·6–2·9 (*m*, methylenes and OH, 7H), 4,1 [*s*, 6H, $(-OCH_3)_2$] and 4·9 (br, CHOH, 1H); (Found: C, 6182; H, 6·12; N, 12·22. $C_{12}H_{14}O_3N_2$ requires: C, 61·55; H, 5·98; N, 11·95%.

Similarly, SBH reduction of the ketone (1a, 1g) gave, after the work-up and recrystallisation from benzene, 4-cyano-1-ethoxy-8-hydroxy-3-methoxy-5,6,7,8-tetrahydroisoquinoline (8a) (920 mg, m.p. 115–117°); NMR (CCl_4): 1·5 (*t*, CH_2–CH_3–, 3H), 1·7–3 (*m*, methylenes and OH, 7H), 4·0 (*s*, $-OCH_3$, 3H), 4·5 (*q*, $-OCH_2$–CH_3, 2H) and 4·8 (br, –CHOH, 1H): (Found: N, 10·92. $C_{13}H_{16}N_2O_3$ requires: N, 11·29%).

3.4. 4-*Cyano*-1,3-*dimethoxy*-8-*hydroxy*-8-*vinyl*-5,6,7,8-*tetrahydroisoquinoline* (1d)

To a stirred solution of vinyl magnesium bromide prepared from Mg (2·88 g) vinyl bromide (16 ml) and dry tetrahydrofuran (50 ml), a solution of azatetralone (1c, 4·6 g) in dry THF (150 ml) was added in an atmosphere of nitrogen at −60–80° (bath temp.) over a period of 30 minutes. The stirring was continued for 2 hr at the same temperature and the reaction mixture was decomposed by dropwise addition of a saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer extracted with ether (3 × 50 ml). The combined organic extracts were washed twice with water and dried. The solvent was removed *in vacuo* to give a gum which crystallised on standing (2·9 g; 55%). A small portion of this was crystallised from benzene-hexane to give the vinyl carbinol (1d, m.p. 110–112°); IR (nujol): ν_{max} 3580 (OH), 2240 (C≡N) and 1600 cm^{-1} (C=C); NMR ($CDCl_3$): 1·65–2·0 (*m*, $2CH_2$ and OH, D_2O exchangeable, 5H), 2·7–3·96 (*m*, benzylic protons, 2H), 4·02 [*s*, $(-OCH_3)_2$, 6H] 4·73 and 5·81 (8 line pattern, 2H, olefinic) and 6·1 (4 line pattern 1H), J_{gem} = 0·9 Hz, J_{trans} = 18 Hz, J_{cis} = 10·8 Hz. (Found: C, 65·01; H, 5·8; N, 10·99. $C_{14}H_{16}N_2O_3$ requires: C, 64·86; H, 5·79; N, 10·8%).

3.5. 4-*Cyano*-1,3-*dimethoxy*-2-*aza*-1,3,5 (10), 9 (11)-*tetraene*-8,14-*seco*-14, 17-*dione* (2)

A mixture of the crude vinyl alcohol (1d, 2·8 g), 2-methylcyclopentane-1,3-dione (2·3 g) and dry triethyl amine (2·1 ml) in dry xylene (150 ml) was refluxed with stirring and azeotropic removal of water for 16 hr. The cooled solution was washed with a 10% solution of NaOH (2 × 30 ml) and then with water (3 × 50 ml). The organic layer was dried and solvent removed *in vacuo*. The residue, thus obtained, on titration with ether gave the seco-dione (2) as solid (3·5 g; 49%) which was recrystallised from benzene-hexane, m.p. 144–46°; IR (nujol): ν_{max} 2240 (C≡N), and 1760 and 1720 cm^{-1} (split C=O); NMR ($CDCl_3$) : 1·19 (*s*, 3H, CH_3), 1·6–2·08 (*m*, 2H), 2·26–3 (*m*, allylic and ketomethylene, 10H), 4·0 [*s*, $(-OCH_3)_2$, 6H] and 6–6·4 (br. t. –C–CH–CH_2, 1H) (Found: C, 67·59; H, 6·4; N, 7·8. $C_{20}H_{22}N_2O_4$ requires: C, 67·79; H, 6·22; N, 7·91%).

3.6. 4-*Cyano*-1,3-*dimeth xy*-2-*azaestra*-1,3,5 (10), 8,14-*pentaen*-17-*one* (3a)

A solution of the seco-dione (2, 3·5 g) and *p*-toluene sulphonic acid (6 g) in a mixture of xylene (200 ml) and dioxane (100 ml) was refluxed for 6 hr in an

atmosphere of nitrogen. The deep red solution, after cooling, was washed with a saturated solution of sodium bicarbonate (3 × 50 ml) and water (3 × 50 ml). The solvent was removed to give the pentaenone (3a) as a gum, which was purified further by chromatography; IR (nujol); ν_{max} 2240 (C≡N) and 1740 cm^{-1} (C=O); NMR ($CDCl_3$): 1·10 (*s*, CH_3, CH), 1·32–3·32 (*m*, 10H), 4·0 [*s*, $(-OCH_3)_2$, 6H] and 5·9 (br.t., –CH–CH_2) (Found: C, 71·22; H, 5·82; N, 7·98. $C_{20}H_{20}N_2O_3$ requires: C, 71·42; H, 5·95; N, 8·33%).

3.7. 4-*Cyano*-1,3-*dimethoxy*-2-*azaestra*-1,3,5 (10), 8,14-*pentaen*-17 *β-ol* (3b)

To a stirred solution of the pentaenone (3a, 1·7 g) in methanol (25 ml) was added $NaBH_4$ (100 mg) in portions. The solution was stirred at room temperature for 3 hr. Acetone (5 ml) was added to quench the reaction. Most of the solvent was removed *in vacuo* and water (100 ml) was added to the residue. The resulting solid was filtered and dried. It was recrystallised from ethanol-water to give 3b (1·6 g), m.p. 220–222°, IR (nujol): ν_{max} 3400–3450 (br, OH), 2240 (C≡N) cm^{-1}; UV (EtOH): λ_{max} 244 (ε, 10540) and 306 nm (35460); NMR ($CDCl_3$): 1·0 (*s*, CH_3, 3H) 1·22–3·1 (*m*, 11H, 10 methylene protons and 1 OH, D_2O exchangeable), 3·9 (*t*, *J* = 9Hz, 17*α* — H, 1H), 3·99, 4·02 [2*s*, $(-OCH_3)_2$, 6H] and 5·55 (br.s., 15H, 1H) (Found: C, 71·48; H, 6·76; N, 8·23. $C_{20}H_{22}N_2O_3$ requires: C, 71·01; H, 6·5; N, 8·3%).

3·8. 4-*Cyano*-1,3-*dimethoxy*-2-*azaestra*-1,3,5 (10), 8-*tetraen*-17 *β-ol* (4)

The pentaenol (3b, 1 g) in thiophene-free benzene (100 ml) was hydrogenated over 10% Pd/$CaCO_3$ (200 mg) catalyst at atmospheric pressure. After the theoretical amount of hydrogen was absorbed the catalyst was filtered off, washed with benzene and the filtrate concentrated *in vacuo*. The solid that was obtained on cooling was recrystallised from benzene, to give 4 (0·7 g), m.p. 180°; UV (EtOH): λ_{max} 288 nm (ε 15130); NMR ($CDCl_3$): 0·81 (*s*, 18-CH_3, 3H), 1·25–2·92 (*m*, methylene protons and 1 OH, D_2O exchangeable), 3·7–3·9 (*t*, *J* = 9Hz, 1H, 17–H), 3·96 and 4·01 [2*s*, $(-OCH_3)_2$, 6H] (Found: C, 70·15; H, 7·45; N, 8·64; $C_{22}H_{24}N_2O_3$ requires: C, 70·6; H, 7·06; N, 8·24%).

3.9. 4-*Cyano*-1,3-*dimethoxy*-2-*azaestra*-1,3,5 (10), 9 (11)-*tetraen*-17 *β-ol* (5)

A solution of the tetraenol (4, 400 mg) in methanol (20 ml) and conc. HCl (4 ml) was refluxed for 16 hr. The solvent was removed *in vacuo* and the residue diluted with water (25 ml) and dried. Recrystallisation of the solid gave 5 as white needles (320 mg), m.p. 210°; NMR ($CDCl_3$): 0·95 (*s*, 18–CH_3, 3H), 1·06–3·4 (*m*, methylene proton and 1OH, 12H), 3·9 (*t*, 17H, 1H), 4·15 [*s*, $(-OCH_3)_2$, 6H], and 6·9 (br.s, –OH, 1H); UV (EtOH): λ_{max} 276 (28900) and 317 nm (9860). (Found: C, 70·2; H, 7·2; N, 8·35, $C_{20}H_{24}N_2O_3$ requires: C, 70·6; H, 7·06; N, 8·24%).

3.10. 4-*Cyano*-1,3-*dimethoxy*-2-*azaestra*-1,3,5-(10)-*trien*-17-*ol* (6a)

The tetraenol (5, 250 mg) in dry ethyl acetate (30 ml) was hydrogenated over Pd/C (10%, 75 mg) catalyst for about 2 hrs. The catalyst was filtered off, washed

with ethyl acetate and the solvent removed from the filtrate. The residue was recrystallised from benzene-hexane to yield 6a (200 mg), m.p. 214–216°; UV (EtOH): λ_{max} 242 (ϵ11640) and 292 nm (12600); NMR ($CDCl_3$): 0·82 (*s*, 18-CH_3, 3H), 1·2–3·4 (*m*, 15H and OH proton (D_2) exchangeable)), 3·8–3·95 (*b*, 1H, 17α-H) and 4·0 [*s*, (-OCH_3)$_2$, 6H] (Found: C, 69·8; H, 7·91; N, 8·4. $C_{22}H_{26}N_2O_3$ requires: C, 70·1; H, 7·6; N, 8·1%).

The acetate (6b) of 6a was prepared in the usual manner by treatment with acetic anhydride and pyridine at room temperature. The acetate (6b) was crystallised from benzene-hexane, m.p. 204–206°; NMR] ($CDCl_3$): 0·85 (*s*, 18-CH_3, 3H), 1–1·85 (*m*, 13H), 2·04 (*s*, -$COCH_3$, 3H), 4·0 [*s*, (-OCH_3)$_2$, 6H] and 4·7 (*t*, 1H, 17α-H) (Found: C, 68·4; H, 7·5; N, 7·1. $C_{22}H_{28}N_2O_4$ requires: C, 68·75; H, 7·29; N, 7·29%).

Acknowledgement

One of the authors (LK) thank the NCERT, Delhi, for financial assistance.

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