Azasteroids. Part X.[1] Synthesis of 3,4-Dihydro-8-methoxybenzo[*c*]-phenanthridin-1(2*H*)-one

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1-Hydroxy- and 1-oxo-1,2,3,4-tetrahydrobenzo[*c*]phenanthridines have been obtained through benzyne cyclisation of anils and reduced anils derived from 5-amino-1-tetralone and appropriate 2-chlorobenzaldehydes.

We report the synthesis of 3,4-dihydro-8-methoxybenzo[*c*]phenanthridin-1(2*H*)-one (IXb) and some of its derivatives: these compounds are analogous to ring-C aromatic steroids [2-4] and may be synthetic precursors to the hitherto unreported 7-azasteroids; they are also similar to the Chelidonium alkaloids,[5] some of which show interesting activities.[5,6] The known synthetic routes [7-17] to benzo[*c*]phenanthridines seemed unlikely to yield the desired substitution pattern, so a route based upon a novel benzyne cyclisation reaction [18,19] was investigated (Scheme).

Tetralin was converted into 5-amino-1-tetralone (II),[20] which was used to prepare the tetralol (III); condensation of this with the aldehyde (Ia) gave the anil (IVa), and benzyne cyclisation of (IVa) gave 1,2,3,4-tetrahydrobenzo[*c*]phenanthridin-1-ol (VIa) in 40% yield. Cyclisation of the reduced anil (VII) proceeded quantitatively to give 1,2,3,4-tetrahydrobenzo[*c*]phenanthridin-1-ol (VIa) rather than expected hexahydro-compound (VIIIa): in (VIIIa), aromatisation is favoured and dehydrogenation occurs during work-up in air. Alcohol (VIa) was readily oxidised [21] to 3,4-dihydrobenzo[*c*]-phenanthridin-1(2*H*)-one (IXa). The ketone (IXa) was also prepared, in 81% yield, by direct cyclisation of the keto-anil (Va).

Cyclisation of the keto-benzylamine (Xa) gave the desired 3,4,5,6-tetrahydrobenzo[*c*]phenanthridin-1(2*H*)-one (XIa) in 88% yield. Treatment of (XIa) with sodium borohydride not only reduced the carbonyl function, but also caused dehydrogenation of ring C, and gave the alcohol (VIa) as the only isolable product (>95%): thus 1,2,3,4,5,6-hexahydrobenzo[*c*]phenanthridin-1-ol (VIIIa) appears to be too unstable to allow isolation.

The 8-methoxy-anils were prepared from 2-chloro-5-methoxybenzaldehyde (Ib) [22] as shown in the Scheme, and cyclisations and interconversions to secure the methoxytetracyclic systems (series b) in various states of oxidation were successful. In contrast to the demethoxy-case, the cyclisation of (Xb) proceeded with spontaneous aromatisation of ring C and only compound (IXb) was isolated; thus neither the oxo- nor the hydroxy-hexahydro-compound could be prepared in the methoxy-series. This variation in the tendency for aromatisation of ring C is puzzling, but may result from changes in the relative stabilities of planar aromatic and flexible 5,6-dihydro-phenanthridines, brought about by different steric interactions with substituents at the 1- and 10-positions.[23] However, why remote groups should have such pronounced effects remains unclear.

Compounds (VIa and b) and (IXa and b), on oral administration to rats, exhibited no significant anabolic, androgenic, or antiandrogenic activity.[24]

EXPERIMENTAL

Microanalyses were performed by L. K. Khullar and B. N. Anand, Panjab University, Chandigarh, India. To prove identity, compounds were compared by t.l.c., mixed m.p., and i.r. spectra (Nujol). Anhydrous sodium sulphate was used as drying agent.

5-Amino-1,2,3,4-tetrahydro-1-naphthol (III).—Reduction of 5-amino-3,4-dihydronaphthalen-1(2*H*)-one [20] (II) with sodium borohydride gave the *5-amino-1-tetralol* (III), m.p. 106—107° (from acetone–petroleum), $\nu_{max.}$ 3390 and 3220 cm^{-1} (OH,NH) (Found: C, 73·65; H, 8·6; N, 8·7. $C_{10}H_{13}NO$ requires C, 73·6; H, 8·05; N, 8·6%).

Formation of Anils.—General procedure. A mixture of *o*-chlorobenzaldehyde (0·351 g) and the aminotetralol (III) (0·408 g) was heated at 120° for 4 h to give *5-[(2-chlorobenzylidene)amino]-1,2,3,4-tetrahydro-1-naphthol* (IVa) (0·35 g, 49%), m.p. 100—102° (from acetone–petroleum), $\nu_{max.}$

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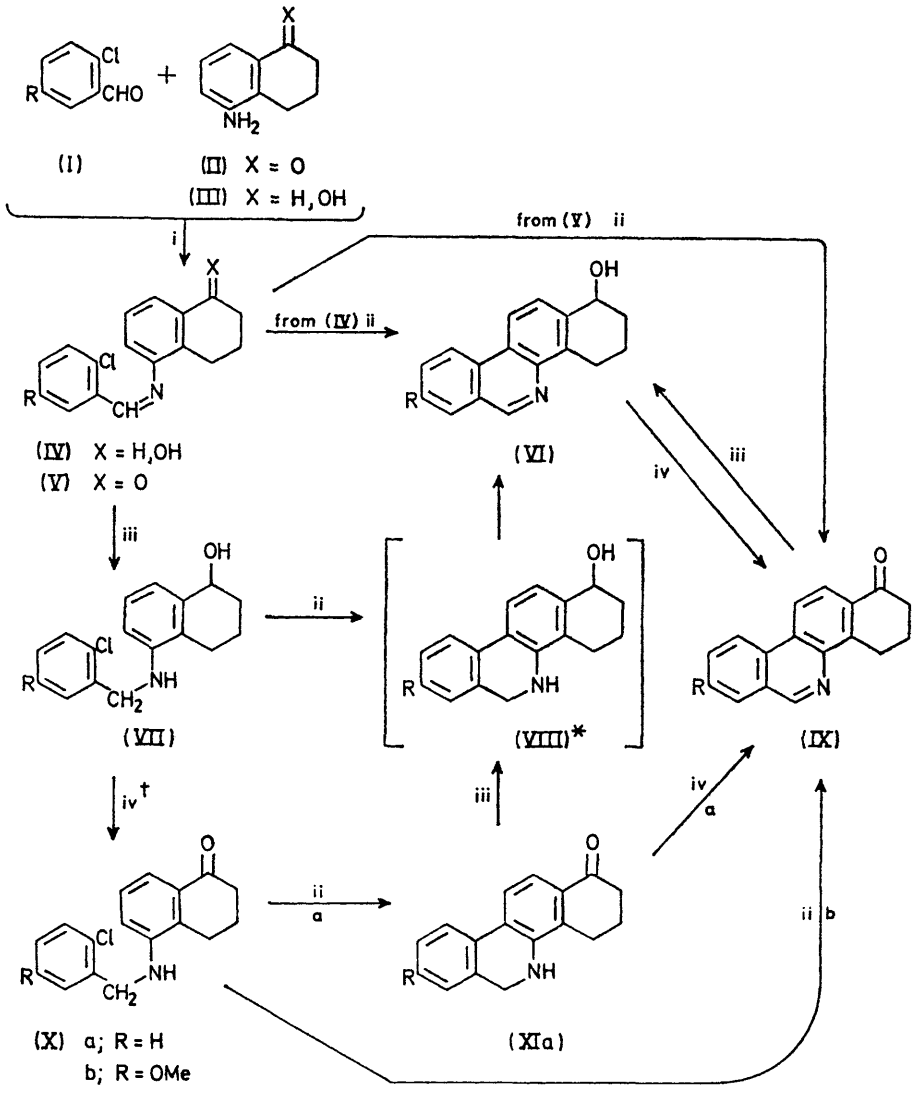

SCHEME

Reagents: i, heat at 120°, 4 h; ii, KNH_2 in NH_3 (liq.); iii, $NaBH_4$; iv, active MnO_2.

* Not isolated. † Required 10 days for (VIIb) ⟶ (Xb).

Compound	M.p. (°C)	Recryst. solvent *	$\nu_{max.}$/cm^{-1}	Analysis: Found (%) C	H	N	Formula	Required (%) C	H	N
(III)	106—107	AP	3390, 3220	73·65	8·6	8·7	$C_{10}H_{13}NO$	73·6	8·05	8·6
(IVa)	100—102	AP	3265, 1620	70·95	5·95	5·3	$C_{17}H_{16}ClNO$	71·45	5·6	4·9
(IVb)	120—121	AP	3340, 3260, 1640	68·1	6·0	4·7	$C_{18}H_{18}ClNO_2$	68·45	5·75	4·45
(Va)	136—137	A	1690, 1635	72·15	5·3	5·45	$C_{17}H_{14}ClNO$	71·95	4·95	4·95
(Vb)	149—150	A	1710, 1645	69·4	5·5	4·8	$C_{18}H_{16}ClNO_2$	68·9	5·15	4·45
(VIa)	185—187	AP	3300, 1615	82·35	6·6	5·8	$C_{17}H_{15}NO$	81·9	6·05	5·6
(VIb)	198—199	AP	3335, 1640	76·95	5·7	5·5	$C_{18}H_{17}NO_2$	77·4	6·15	5·0
(VIIa)	104—105	AP	3550, 3430	71·35	6·3	4·9	$C_{17}H_{18}ClNO$	70·85	6·3	4·85
(VIIb)	117—118	AP	3530, 3425	68·55	6·3	4·9	$C_{18}H_{20}ClNO_2$	68·05	6·35	4·4
(IXa)	198—200	A	1665	82·7	5·5	5·95	$C_{17}H_{13}NO$	82·55	5·3	5·65
(IXb)	206—207	A	1700, 1640	78·35	5·2	5·25	$C_{18}H_{15}NO_2$	77·95	5·45	5·05
(Xa)	142—143	AP	3435, 3395, 1665	71·3	5·9	4·9	$C_{17}H_{16}ClNO$	71·45	5·6	4·9
(Xb)	113—114	EP	3405, 1695	69·05	6·2	4·7	$C_{18}H_{18}ClNO_2$	68·45	5·75	4·45
(XIa)	187—189	AP	3395, 1670	81·35	6·2	5·75	$C_{17}H_{13}NO$	81·9	6·05	5·6

* A = acetone, AP = acetone–petroleum, EP = ether–petroleum.

3265 (OH) and 1620 cm^{-1} (Found: C, 70·95; H, 5·95; N, 5·3. $C_{17}H_{16}ClNO$ requires C, 71·45; H, 5·6; N, 4·9%).

Benzyne Cyclisations.—General procedure. The anil (IVa) (0·143 g) in ether * (5 ml) was added to stirred potassium amide [from potassium (0·117 g)] in liquid ammonia (150 ml). After 45 min ammonium chloride (0·3 g) was added and ammonia was allowed to escape. Water was added and the residue was extracted with ether (3 × 25 ml); the extract was washed, dried, and evaporated to give a gummy complex residue (t.l.c.) which afforded 1,2,3,4-*tetrahydrobenzo*[c]*phenanthridin*-1-*ol* (VIa) (0·05 g, 40%), m.p. 185—187° (from acetone–petroleum), $\nu_{max.}$ 3300 (OH) and 1615 cm^{-1} (Found: C, 82·35; H, 6·6; N, 5·8. $C_{17}H_{15}NO$ requires C, 81·9; H, 6·05; N, 5·6%).

Other anils and phenanthridines were prepared by these procedures; reductions with sodium borohydride and oxidations with manganese dioxide [21] were carried out by standard methods. The data for compounds prepared are in the Table.

* Compound (X) dissolved in ether–tetrahydrofuran, (IVb) in tetrahydrofuran.

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