834. *Optical Rotatory Dispersion. Part XXII.*[1] *Steroidal Azomethines*

By R. Bonnett and T. R. Emerson

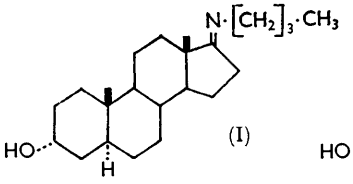
The formation of steroidal Schiff's bases possessing exocyclic azomethine groups at the 3-, 16-, and 17-positions has been examined. Compounds of the last type can be readily isolated, but in less-hindered situations the azomethine group is much more sensitive. Spectral and optical rotatory dispersion data are presented and discussed.

Although the reaction of cyclic ketones with primary amines to give azomethines is well known,[2] surprisingly little has been reported on steroidal azomethines formed in this way. Certain steroidal ketones have been shown to give azomethines with ethanolamine,[3]

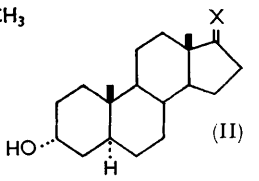
[1] Part XXI, preceding Paper. This Paper is Part II of the Series on the Optical Rotatory Dispersion of Azomethines: for Part I, see preceding Paper.
[2] E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. Trav. chim.*, 1952, **71**, 168.
[3] K. Irmscher, *Chem. Ber.*, 1962, **95**, 907.

but this particular reaction can be complicated by partial or complete cyclisation to the spiro-oxazolidine system.[4] Schiff's bases derived from steroidal ketones and simple alkylamines appear to have been little studied. Such compounds were required for optical rotatory dispersion (o.r.d.) studies and have now been prepared using a molecular sieve to drive the reaction to completion.

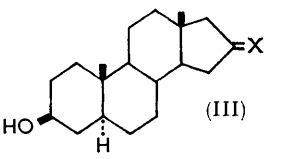
The reaction of 5α-cholestan-3-one with n-butylamine at room temperature was followed by infrared spectroscopy; after four days the crude product showed a strong peak at 1655 cm.$^{-1}$ (azomethine stretching mode) together with a weak band in the carbonyl region. s-Butylamine behaved similarly, but no reaction with t-butylamine was detected under these conditions. However, efforts to purify azomethines derived from 5α-cholestan-3-one were unsuccessful. A variety of reaction pathways is open to such compounds with unhindered enaminisable azomethine functions, and during the prepartion, or on storage, the substances became coloured.



(I)



(II)



(III)

Attention was therefore transferred to a keto-group at a more hindered site in the steroidal framework since it would be expected, on the basis of the stabilities [5] of the steroidal nitrimines (the 3-nitrimines are less stable than the 12- and 20-nitrimines), that such a group would give less sensitive azomethines. The 17-position was selected, and it was found that androsterone (3α-hydroxy-5α-androstan-17-one) slowly reacted with n-butylamine. Moreover, the product showed little or no tendency to decompose on storage. It is formulated as *N*-(3α-hydroxy-5α-androstan-17-ylidene)-n-butylamine (I) on the basis of its elemental analysis and spectral properties. The infrared spectrum had bands at 3300 (OH) and 1665 cm.$^{-1}$ (C=N) but had no carbonyl absorption, while the n.m.r. spectrum had a broadened triplet at 6·79 τ corresponding to two protons (=N·CH_2–), cf. the C-5 protons of 2,4,4-trimethyl-1-pyrroline.[6] In the ultraviolet (ethanol) the compound showed a broad band, ascribable to the $n \rightarrow \pi^*$ transition of the azomethine group,[7] at 238 mμ (ε 220). On treating the solution with a trace of acid this band disappeared ($>\dot{C}=\dot{N}- \rightarrow >C=\overset{+}{N}H-$) and was partly replaced by strong end-absorption (Figure 1); basification regenerated the original absorption. Such behaviour has also been observed with other unconjugated azomethines.[7] Tautomerisation to the enamine may account for some of the observed absorption but cannot be very important since tertiary enamines are known to absorb strongly in this region [8] and secondary enamines would be expected to show somewhat similar absorption. In aqueous ethanol at 20° the steroidal azomethine was slowly hydrolysed (Figure 2). The azomethine band diminished following first-order kinetics ($t_{0·5}$ ~35 hr.) while the much weaker carbonyl absorption correspondingly developed until it approached the intensity of that of androsterone (ε 40), which was indeed isolated from the cell.

n-Propylamine also gave an azomethine derivative with androsterone, but reactions with the more hindered s-butylamine and t-butylamine were not observed.

[4] E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Amer. Chem. Soc.*, 1953, **75**, 358.
[5] S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J.*, 1958, 4614, and references therein.
[6] R. Bonnett and D. E. McGreer, *Canad. J. Chem.*, 1962, **40**, 177.
[7] R. Bonnett, N. J. David, J. Hamlin, and P. Smith, *Chem. and Ind.*, 1963, 1836; R. Bonnett, *J.*, 1965, 2313.
[8] K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J.*, 1946, 45.

A related 16-oxo-steroid, 3β-hydroxy-5α-androstan-16-one, reacted with primary amines more readily than did androsterone. n-Butylamine, for example, reacted at room temperature in less than one day; s-butylamine also reacted although it required refluxing for many hours. The azomethines formed from the 16-oxo-steroid were difficult to purify, however, and yields of the purified products were low. Partial hydrolysis to regenerate

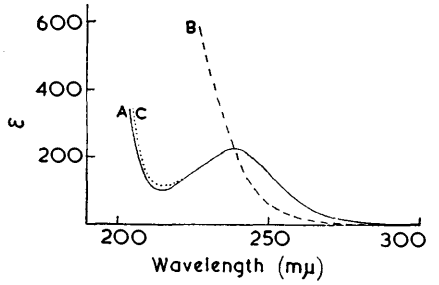


FIGURE 1. Effect of protonation on the ultraviolet spectrum of *N*-(3α-hydroxy-5α-androstan-17-ylidene)-n-butylamine (I). A, (I) in ethanol. B, Ethanolic solution treated with a trace of 6N-HCl. C, (dotted line) Solution B treated with a trace of aqueous ammonia.

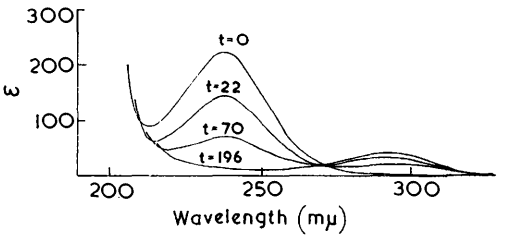


FIGURE 2. Hydrolysis of *N*-(3α-hydroxy-5α-androstan-17-ylidene)-n-butylamine in 20% aqueous ethanol at 20°. Time *t* in hr.

the ketone, easily recognised in the infrared and o.r.d. measurements, occurred during crystallisation of the *N*-methyl derivative. Because of these difficulties analyses were not obtained in all cases.

O.r.d. data for steroidal ketones and their related azomethines

Compound	Solvent	First extremum (peak) [φ]	First extremum (peak) λ (mμ)	Second extremum (trough) [φ]	Second extremum (trough) λ (mμ)	Amplitude *a*
II; X = O)	Hexane	+5910	320	−6250	275	+122
	MeOH	+7350	313	−7080	276	+144
(II; X = N·[CH_2]$_3$·CH_3)	Hexane	+3100	262	−2090	228	+52
	MeOH	+4880	246	−1420	220	+63
(II; X = N·[CH_2]$_2$·CH_3...	Hexane	+3910	263	−940	228	+49 *
	MeOH	+4680	250	−910	220	+56

Compound	Solvent	First extremum (trough) [φ]	First extremum (trough) λ (mμ)	Second extremum (peak) [φ]	Second extremum (peak) λ (mμ)	Amplitude *a*
(III; X = O)	Hexane	−8550	323	+9400	266	−180
	MeOH	−11,900	316	+11,400	282	−233
(III; X = N·[CH_2]$_3$·CH_3)	Hexane	−5200	269	+3630	230	−88
	MeOH	−6570	254	+5200	219	−118
(III; X = N·CHMe·Et)...	Hexane	−4380	266	+1520	233	−59 *
	MeOH	−6450	256	+4100	221	−106
(III; X = NMe)	Hexane	−3800	270	+4480	230	−83 †

* Azomethine only partially soluble; values given are approximate. † Some ketone present as impurity; values given are approximate.

The Table summarises the o.r.d. results obtained with steroidal azomethines; the corresponding ketones are included for comparison.

The extrema occur at *ca.* 250 and 220 mμ in methanol as would be expected from the ultraviolet maxima of the compounds, which occur at *ca.* 235 mμ. In hexane the extrema are displaced to higher wavelengths. The amplitudes are larger in methanol than in hexane, but both values are lower than the amplitudes of the corresponding ketones. The

signs of the Cotton effects of the azomethines are the same as those of the corresponding ketones, while the length of the alkyl chain on the nitrogen atom makes little difference to the amplitude.

Experimental

O.r.d. measurements were made at 20—25° with the Bellingham and Stanley/Bendix-Ericsson spectropolarimeter "Polarmatic 62." Concentrations were in the range 0·2—0·6 mg./ml. I.r. spectra were recorded on a Perkin-Elmer Infracord spectrophotometer.

N-(3α-*Hydroxy*-5α-*androstan*-17-*ylidene*)-*n*-*butylamine* (I).—(*a*) *Preparation.* A mixture of androsterone (55 mg.), molecular sieve (4A, Linde; 0·5 g.), and n-butylamine (2 ml.; freshly distilled) was kept under nitrogen in the dark at room temperature for 3 weeks. The supernatant liquid and washings of the sieve (3 ml. n-butylamine) were filtered through a kieselguhr pad. The solvent was removed from the filtrate under reduced pressure, and the residual solid was crystallised from hexane at −10° to give 51 mg. (78%) of N-(3α-*hydroxy*-5α-*androstan*-17-*ylidene*)-*n*-*butylamine*, rosettes of needles, m. p. 142—143° (Found: C, 79·95; H, 11·1; N, 4·45. $C_{23}H_{39}NO$ requires C, 79·95; H, 11·4; N, 4·05%), $\nu_{max.}$ (Nujol) 3300, 1665 cm.$^{-1}$, τ ($CDCl_3$) (tetramethylsilane internal standard) 5·96 (1H); 6·79 (2H); 7·5—9·1 (~30H); 9·20 (~6H), $\lambda_{max.}$ (hexane) 248 mμ (log ε 2·24), $\lambda_{max.}$ (EtOH) 238 mμ (log ε 2·34). The *picrate*, needles, had m. p. 192—193° from ethanol (Found: C, 60·9; H, 7·4; N, 9·7. $C_{29}H_{42}N_4O_8$ requires C, 60·6; H, 7·4; N, 9·75%), $\nu_{max.}$ (Nujol) 3290, 1690 cm.$^{-1}$.

(*b*) *Hydrolysis.* The azomethine (16 mg.) was dissolved in 20% aqueous ethanol (v/v; 12 ml.) and the ultraviolet spectrum was observed at intervals. The 238 mμ band gradually disappeared and a weaker band at 291 mμ emerged (Figure 2). After 200 hr. the ethanol was removed (water-bath), the liquid residue was cooled, and the solid was collected. Recrystallisation from hexane gave androsterone (6 mg.) identified by mixed m. p. and infrared comparison with the authentic sample.

N-(3α-*Hydroxy*-5α-*androstan*-17-*ylidene*)-*n*-*propylamine* (II).—A mixture of androsterone (50 mg.), n-propylamine (3 ml.), and molecular sieve was refluxed gently for 30 hr. The supernatant liquid and washings (3 ml. n-propylamine) were evaporated under reduced pressure with gentle warming to give a white solid which, after crystallisation from hexane, had m. p. 159—161° (Found: C, 79·3; H, 11·1; N, 4·2. $C_{22}H_{37}NO$ requires C, 79·7; H, 11·2; N, 4·2%), $\nu_{max.}$ (CCl_4) 3690, 3350, 1685 cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 235 mμ (log ε ~2·41).

N-(3β-*Hydroxy*-5α-*androstan*-16-*ylidene*)-*n*-*butylamine* (III).—A mixture of 3β-hydroxy-5α-androstan-16-one (64 mg.) and n-butylamine (3 ml.) was kept at room temperature over molecular sieve for 21 hr. The product, obtained as above, had m. p. 127—129° (Found: C, 79·1, 80·2; H, 11·3, 10·4; N, 4·4, 4·1. $C_{23}H_{39}NO$ requires C, 80·0; H, 11·4; N, 4·1%), $\nu_{max.}$ (CCl_4) 3680, 3300, 1685 cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 235 mμ (log ε 2·35).

N-(3β-*Hydroxy*-5α-*androstan*-16-*ylidene*)-*s*-*butylamine* (IV).—3β-Hydroxy-5α-androstan-16-one (37 mg.) and s-butylamine (3 ml.) were refluxed together over molecular sieve for 28 hr. The product, obtained as above, had m. p. 211·5—214°, $\nu_{max.}$ (CCl_4) 3600, 3300, 1680 cm.$^{-1}$.

N-(3β-*Hydroxy*-5α-*androstan*-16-*ylidene*)*methylamine* (V).—3β-Hydroxy-5α-androstan-16-one (33 mg.) and molecular sieve were treated with liquid methylamine at −45°. The reaction tube was securely stoppered, and kept at room temperature for 5 days. The methylamine was then allowed to evaporate and the residue, after crystallisation from hexane, had m. p. 168—172°, $\nu_{max.}$ ($CHCl_3$) 3600, 3400sh, 1685 cm.$^{-1}$.

A research grant from the Smith, Kline and French Research Institute is gratefully acknowledged. We thank Professor W. Klyne for his interest, Mr. R. J. Swan for making the o.r.d. measurements, and the Medical Research Council Steroid Reference Collection for providing some of the steroids.

Chemistry Department, Westfield College, London N.W.3.
Chemistry Department, Queen Mary College,
London E.1.

[*Received, December 23rd*, 1964.]