New Steroidal Heterocycles: Androstano[3,2-*b*](pyrimido[1,2-*a*]benzimidazoles)

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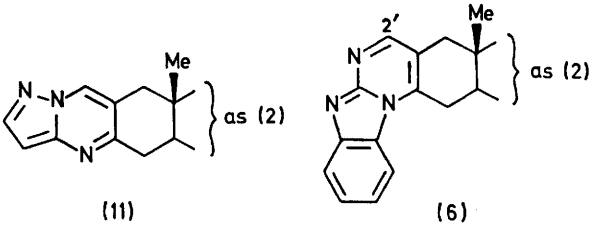
The preparation of steroidal heterocycles containing the pyrimido[1,2-*a*]benzimidazole ring system fused to the 2,3-position of the steroid nucleus is described. These are prepared by the reaction of 2-aminobenzimidazole with 2-hydroxymethylene-3-oxo-steroids.

As a part of our studies directed towards the development of new aza-steroids of biological interest,[1] we report the results of the reaction of 2-aminobenzimidazole with steroidal β-ketoaldehydes.

RESULTS AND DISCUSSION

The condensation of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (2) with 2-aminobenzimidazole (1) in absolute ethanol gives a product, m.p. 268—270 °C (decomp.) in 87% yield. The i.r. spectrum of this product does not show any carbonyl absorption; it thus appears that the product has either structure (6) or (7), both consistent with the molecular formula $C_{28}H_{35}N_3O$, obtained by elemental analysis and high-resolution mass spectrometry. However, the ^1H and ^{13}C n.m.r. evidence favours structure (7), namely 17β-hydroxy-17α-methyl-5α-androstano[3,2-*b*](pyrimido-[1,2-*a*]benzimidazole).

The ^1H n.m.r. spectrum of the condensation product (7) exhibits signals at δ 0.80 (s, 3 H, 18-Me), 0.90 (s, 3 H, 19-Me), 1.24 (s, 3 H, 17-Me), 7.14—7.90 (m, 4 H, 6′-, 7′-, 8′-, and 9′-H), and 8.34 (s, 1 H, 4′-H). The signal at δ 8.34 corresponding to 4′-H is found to be fairly broadened by long-range coupling with the methylene protons at position 1. The assignment of the linear structure (7) is consistent with the observations made in our previous publications [1d,e] that in the linearly fused pyrazolo[1,5-*a*]pyrimidines (11) and *s*-triazolo[1,5-*a*]pyrimidines (12), the signal for the proton



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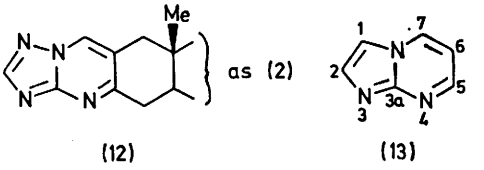

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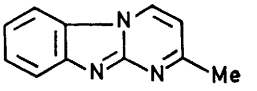
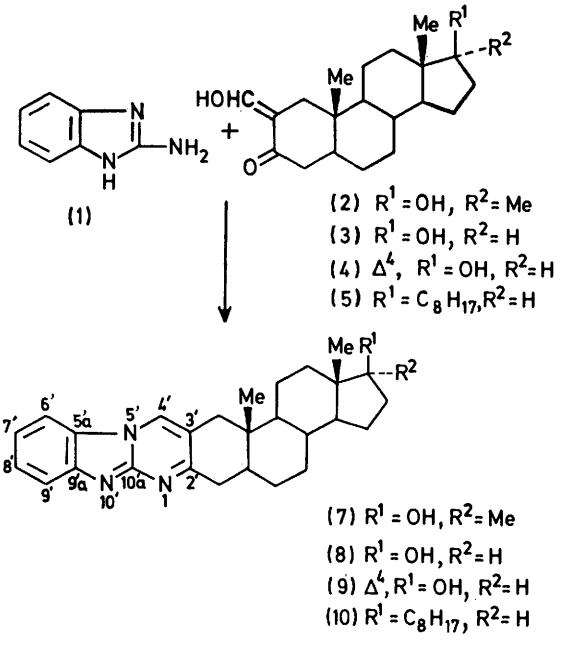


(14)

of the pyrimidine ring in the ^1H n.m.r. spectrum is broadened by a small long-range coupling with the protons at position 1. The alternative structure (6) for the steroidal condensation product is discounted, since it would be expected [1d,e] to show a sharp singlet for the 2′-H due to the absence of any long-range coupling.

The assignment of structure (7) is also supported by ^{13}C n.m.r. evidence. The ^{13}C chemical shifts of the aromatic ring carbons of the pyrimidobenzimidazole (7), along with those of imidazo[1,2-*a*]pyrimidine (13) [2] and 2-methylpyrimido[1,2-*a*]benzimidazole (14),[1c] are given in the Table. The assignment of the chemical shifts for six of the ring carbons in the compounds (7) and (14) is based upon the comparison of the spectra of these two compounds and the ^{13}C chemical shifts of imidazo[1,2-*a*]pyrimidine (13).[2] It is also noted [2] that in nitrogen heterocyclic systems, the carbons bonded to



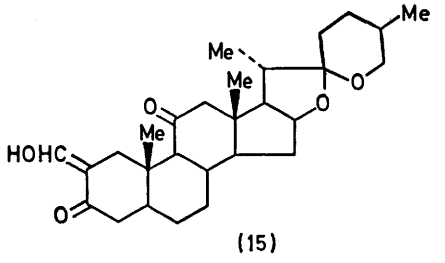
nitrogen atoms are appreciably deshielded relative to benzene, whilst the nitrogen atoms at bridgehead positions have little effect on the adjacent carbon atoms due to significant delocalisation of the lone pair of electrons. The specific assignment of the remaining carbon resonances, (6′—9′-C), although not important as far as the distinction between structures (6) and (7) is concerned,

^{13}C Chemical shifts of the aromatic ring carbons (δ from $SiMe_4$)

Compound	2′-C	3′-C	4′-C	5′a-C	9′a-C	10′a-C
(7) [a]	165.90	115.80	130.65	126.39	144.28	150.28
(14) [b]	165.72	107.43	132.75	126.75	144.14	150.59
(13)	150.94	109.41	136.04	112.66	135.14	148.86
	(5-C)	(6-C)	(7-C)	(1-C)	(2-C)	(3a-C)

[a] ^{13}C Chemical shifts of 6′-C to 9′-C (δ 110.18, 119.84, 120.69, and 125.59) not assigned. [b] ^{13}C-Chemical shifts of 6′-C to 9′-C (δ 110.13, 120.17, 121.32, and 125.83) not assigned.

is not possible from the above information alone; nevertheless these carbon resonances can be readily distinguished from the other carbon resonances. The chemical shift of 4′-C (δ 130.65) in the condensation product (7) correlates well with the chemical shift of 7-C (δ 136.04) in imidazo[1,2-*a*]pyrimidine (13) and with the chemical shift of 4-C (δ 132.75) in 2-methylpyrimido-[1,2-*a*]benzimidazole (14), thus confirming a linear fusion of the steroid to the heterocyclic system. If the



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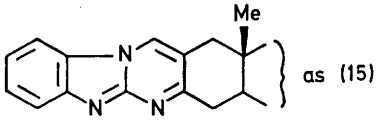

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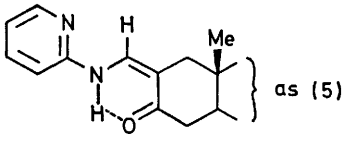

(17)

product had the angular structure (6) the chemical shift of 2′-C would have been expected to be in the region of δ 150.94 which is the chemical shift of 5-C in the imidazo[1,2-*a*]pyrimidine (13).

Under analogous reaction conditions, the condensation of 2-aminobenzimidazole (1) with 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3), 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4), 2-hydroxymethylene-5α-cholestan-3-one (5), and 2-hydroxymethylene-5α-spirostan-3,11-dione (15) gave 17β-hydroxy-5α-androstano[3,2-*b*](pyrimido[1,2-*a*]benzimidazole) (8), 17β-hydroxyandrost-4-eno[3,2-*b*](pyrimido[1,2-*a*]benzimidazole) (9), 5α-cholestano[3,2-*b*](pyrimido[1,2-*a*]benzimidazole) (10), and 11-oxo-5α-spirostano[3,2-*b*](pyrimido[1,2-*a*]benzimidazole) (16), respectively. The preparation of the compound (10) was previously reported by Antaki and Petrow,[3] but no spectroscopic evidence was given for its structure. All the steroidal pyrimidobenzimidazoles reported in this paper are formed through pathway (b) of the reaction mechanism shown in our previous publication.[1b] Further support for this pathway is afforded by the reaction of 2-[(2-pyridylamino)-methylene]-5α-cholestan-3-one (17) with 2-aminobenzimidazole (1), leading to the product (10).

EXPERIMENTAL

M.p.s were determined on Gallenkamp apparatus. I.r. spectra were recorded in bromoform on a Perkin-Elmer 157G spectrometer, and ^{1}H n.m.r. spectra in deuteriochloroform using $SiMe_4$ as internal standard on Nuclear Magnetic Resonance Ltd. EM 360 (60 MHz) or Varian HA 100 (100 MHz) spectrometers. Mass spectrometry was carried out on AEI MS 902 instrument. ^{13}C N.m.r. spectra were obtained in deuteriochloroform solutions on a Varian CFT-20 n.m.r. spectrometer operating at 20—80 MHz in the Fourier-transform mode at a probe temperature of 30 °C.

All the starting steroidal β-ketoaldehydes were prepared by known literature methods.

General Procedure for the Condensation Reactions.—A solution of a 2-hydroxymethylene-3-oxo-steroid (1×10^{-3} mol) and 2-aminobenzimidazole (1) (1.2×10^{-3} mol) in absolute ethanol (50 ml) was refluxed for 7 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue was chromatographed over alumina. Elution with chloroform gave a yellow solid which was recrystallised from a suitable solvent.

17β-*Hydroxy*-17α-*methyl*-5α-*androstano*[3,2-b](*pyrimido*-[1,2-a]*benzimidazole*) (7) was recrystallised from chloroform–ethanol to give fine yellow crystals (87%), m.p. 268—270 °C (decomp.); $\nu_{max.}$ 3 600 (OH), 1 635, 1 605, 1 510, 1 450, 1 415, 925, and 730 cm^{-1}; δ 0.80 (s, 3 H, 13-Me), 0.90 (s, 3 H, 10-Me), 1.24 (s, 3 H, 17-Me), 7.14—7.90 (m, 4 H, 6′—9′-H), and 8.34 (s, 1 H, 4′-H) (Found: C, 78.55; H, 8.4; N, 9.5%; M^+, 429.277 705. $C_{28}H_{35}N_3O$ requires C, 78.27; H, 8.22; N, 9.79%; *M*, 429.277 998).

17β-*Hydroxy*-5α-*androstano*[3,2-b](*pyrimido*[1,2-a]*benz-imidazole*) (8) was recrystallised from acetone to give yellow crystals (75%), m.p. 284—286 °C (decomp.); $\nu_{max.}$ 3 590 (OH), 1 635, 1 605, 1 510, 1 450, 1 415, 1 050, 760, and 730 cm^{-1}; δ 0.80 (s, 6 H, 10- and 13-Me), 3.70 (m, 1 H, 17-H), 7.18—8.05 (m, 4 H, 6′—9′-H), and 8.40 (s, 1 H, 4′-H) (Found: C, 78.25; H, 8.15; N, 10.2%; M^+, 415.262 356. $C_{27}H_{33}N_3O$ requires C, 78.02; H, 8.01; N, 10.62%; *M*, 415.262 349).

17β-*Hydroxyandrost*-4-*eno*[3,2-b](*pyrimido*[1,2-a]*benz-imidazole*) (9) was recrystallised from ethanol to give yellow crystals (70%), m.p. 198—200 °C; $\nu_{max.}$ 3 590 (OH), 1 635, 1 580, 1 505, 1 450, 1 430, 1 215, 1 060, 1 040, 870, 765,

and 735 cm^{-1}, δ 0.82 (s, 3 H, 13-Me), 1.05 (s, 3 H, 10-Me), 3.65 (m, 1 H, 17-H), 6.40 (s, 1 H, 4-H), 7.10—8.96 (m, 4 H, 6′—9′-H), and 8.28 (s, 1 H, 4′-H) (Found: C, 78.1; H, 7.6; N, 9.9%; M^+, 413.246 104. $C_{27}H_{31}N_3O$ requires C, 78.40; H, 7.56; N, 10.17%; *M*, 413.246 700).

5α-*Cholestano*[3,2-b](*pyrimido*[1,2-a]*benzimidazole*) (10) was recrystallised from chloroform–ethanol to give yellow crystals (71%), m.p. 290—292 °C (lit.[3] m.p. 295 °C); $\nu_{max.}$ 1 630, 1 605, 1 510, 1 445, and 770 cm^{-1} (Found: C, 82.0; H, 9.45; N, 8.1%; M^+, 511.392 114. $C_{35}H_{49}N_3$ requires C, 82.13; H, 9.73; N, 8.17%; *M*, 511.392 629). The ^1H n.m.r. spectrum could not be obtained because of its highly insoluble nature.

11-*Oxo*-5α-*spirostano*[3,2-b](*pyrimido*[1,2-a]*benzimidazole*) (16) was recrystallised from ethanol to give yellow crystals (78%), m.p. 310—312 °C; $\nu_{max.}$ 1 695 (CO), 1 635, 1 610, 1 510, 1 450, 1 420, 1 045, 975, 915, 890, 760, and 730 cm^{-1}; δ 0.74 (s, 3 H, 13-Me), 1.00 (s, 3 H, 10-Me), 7.20—8.94 (m, 4 H, 6′—9′-H), and 8.30 (s, 1 H, 4′-H) (Found: C, 75.85; H, 7.85; N, 7.55%; M^+, 533.329 658. $C_{35}H_{43}N_3O_3$ requires C, 75.90; H, 7.83; N, 7.59%; *M*, 533.330 429).

The Reaction of 2-[(2-*Pyridylamino*)*methylene*]-5α-*cholestan*-3-*one* (17) *with* 2-*Aminobenzimidazole* (1).—A solution of 2-[(2′-pyridylamino)methylene]-5α-cholestan-3-one (17) [1d] (0.49 g, 1×10^{-3} mol) and 2-aminobenzimidazole (1) (0.158 g, 1.2×10^{-3} mol) in dry toluene (30 ml) containing toluene-4-sulphonic acid (20 mg) was refluxed for 5 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue chromatographed over alumina. Elution with chloroform and recrystallisation of the eluate from ethanol–chloroform gave yellow crystals (0.36 g, 72%), m.p. 290—292 °C, identical (m.p. and i.r.) with 5α-cholestano[3,2-*b*](pyrimido[1,2-*a*]benzimidazole) (10).

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