Synthesis of 17β-(2-Amino-oxazol-4-yl)-steroids

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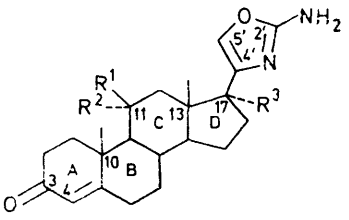
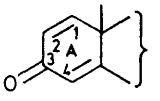
The reaction of cyanamide with the 20-oxo-21-hydroxy-side-chain of corticosteroids in methanolic aqueous ammonia yields the title compounds.

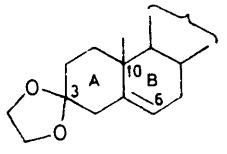
PREVIOUS attempts to obtain 17β-(amino-oxazolyl)-steroids, by reaction carried with cyanamide in acidic medium,[1] or, for example from 21-iodocortisone with urea in dimethylformamide,[2] have failed; however we



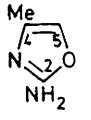
(1) $R^1 = R^2 = R^3 = H$
(2) $R^1R^2 = O, R^3 = OH$
(3) $R^1 = R^3 = OH, R^2 = H$



(4) $R^1R^2 = O, R^3 = OH$
(5) $R^1 = R^3 = OH, R^2 = H$



(6) $R^1R^2 = O, R^3 = OH$



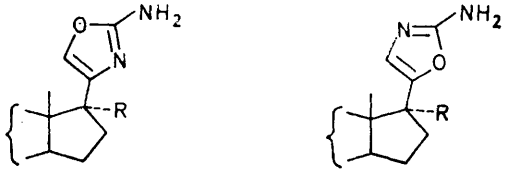
(7)

have obtained good results by applying the reaction with cyanamide, but in the presence of ammonia, to steroids with a 17-(α-ketol) side-chain. Sanchez *et al.*[3] have recently applied this reaction to some pentoses, but obtained only 2-amino-oxazoline derivatives. From cortexone, cortisone, cortisol, prednisone, prednisolone, and cortisone 3-ethylene acetal we obtained the 17β-(2-amino-oxazol-4-yl)androstane derivatives (1)—(6), respectively.

The simple 2-amino-4-methyl oxazole (7), which has been a useful model for interpreting the i.r. and ^1H n.m.r. data of compounds (1)—(6), was recently synthesised from cyanamide and hydroxyacetone in aqueous media (as an oil, b.p. 79—81° at 2 mmHg; no spectroscopic data were reported);[4] we prepared it both by the literature method and under our own conditions as a solid, m.p. 28—29°, preservable under nitrogen and purifiable by sublimation.

The amino-oxazoles (1)—(6) were identified by their analytical and spectral data. The i.r. spectra (KBr) showed complex patterns owing to strong hydrogen bonding (high m.p.s), but in solution spectra ($CHCl_3$) the amino-group stretching frequencies were easily identified (*ca.* 3 510 and 3 415 cm^{-1}). Hence as in other 2-amino-oxazole derivatives[1,5] the amino-form predominates. 2-Amino-4-methyloxazole (7) also shows maxima at 1 643, 1 615, and 1 574 cm^{-1} which can be assigned to NH_2 scissoring and two ring modes, highly mixed;[1,6] in the spectra of compounds (1)—(6) the C-20 carbonyl stretching frequency of the parent steroids[7] is absent and new bands closely similar to those of (7) appear in the 1 645—1 570 cm^{-1} range ($CHCl_3$). The 1 640 cm^{-1} absorption, not well resolved from the C-3 carbonyl stretching band, appears as a very strong band in the spectrum of the 3-acetal (6).

Conversion into the amino-oxazolyl derivatives is invariably accompanied by a negative shift in optical rotation. The reaction only occurs when the 20-oxo-21-hydroxy-side-chain is present; 17α-hydroxypregn-4-ene-3,20-dione (17α-hydroxyprogesterone), lacking a 21-hydroxy-group, does not react. One might expect that the resulting 17β-amino-oxazole ring could be 4- or 5-substituted[8] [(a) or (b)]; however the crude



R = H or OH

(a) (b)

derivatives do not appear to be isomeric mixtures. T.l.c. shows only one spot, which gives a reddish colour,

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characteristic of the heterocyclic ring, with 2,6-dichlorobenzoquinone *N*-chloroimide (a blue colour is observed for oxazoline derivatives);[3] and in the ^{1}H n.m.r. spectra of the isolated compounds the integrated resonance of the signal assigned to the oxazole ring hydrogen agrees exactly with one proton. The problem of attributing structure (a) or (b) to our compounds was solved by the n.m.r. data (Table).

^{1}H N.m.r. data (τ values; Me_4Si internal standard) *

Compound	Proton(s)	$(CD_3)_2SO$	$CF_3{\cdot}CO_2H$ †	$CDCl_3$
(1)	5′-H	3.05 (s)	2.92 (s)	3.20 (d, *J* 0.9 Hz) ‡
	2′-NH_2	3.73 (s)	2.75br (s)	5.0br (s)
(2)	5′-H	2.92 (s)	2.78 (s)	
	2′-NH_2	3.65 (s)	2.55br (s)	
(3)	5′-H	2.98 (s)	2.76 (s)	
	2′-NH_2	3.72 (s)	2.6br (s)	
(4)	5′-H	2.91 (s)	2.78 (s)	
	2′-NH_2	3.64 (s)	2.53br (s)	
(5)	5′-H	2.95 (s)	2.79 (s)	
	2′-NH_2	3.68 (s)	2.55br (s)	
(6)	5′-H	2.94 (s)		
	2′-NH_2	3.67 (s)		
(7)	5-H	3.01 (q, *J* 1.4 Hz)	2.95 (q, *J* 1.4 Hz)	3.17 (q, *J* 1.4 Hz)
	4-CH_3	8.14 (d, *J* 1.4 Hz)	7.80 (d, *J* 1.4 Hz)	8.00 (d, *J* 1.4 Hz)
	2-NH_2	3.6 (s)	2.7br (s)	4.8br (s)

* All the compounds show the expected data for the non-side-chain protons (ref. 7). † In our spectra, the (3)N$^+$H resonance was detectable only for compound (1) as a very broad signal at τ −0.3 (the solvent signal covers the range τ −0.5 to −2). ‡ Coupled with 17α-H.

The 5-H signal of the model oxazole (7) ($CDCl_3$) lies at almost the same τ value as that of the 5′-H in (1), whereas the 4-H resonance in benzyl 5-methyloxazol-2-ylcarbamate occurs at τ 3.60 in the same solvent;[9] the paramagnetic shift of 0.40—0.43 p.p.m. is due to deshielding by the vicinal nuclear oxygen.[1,10] Compounds (2)—(6) are not soluble enough in $CDCl_3$ for a useful comparison, but this is possible in $(CD_3)_2SO$; in this solvent, the 5-H signal for (7) lies at τ 3.01 and the 5′-H signal for (1) at τ 3.05; for compounds (2)—(6) this signal, in the same solvent, is found at τ 2.91—2.98. This small paramagnetic shift from the value for (1) is probably due to the effect of the neighbouring 17α-OH, present in all the latter compounds.

Further, conclusive data supporting structure (a), come from the spectra in trifluoroacetic acid: the 4-H resonance of 2-cyanoamino-5-methyloxazole lies at τ 2.45, whereas the 5-H signal of the 4-methyl isomer is at τ 2.72 (ref. 3), and that of (7) occurs at τ 2.95 in the same solvent. This the 4-H resonance in oxazoles and amino-oxazoles shifts more to lower field than that of the 5-H because protonation always occurs on the ring nitrogen atom.[1,9-11] In our steroidal derivatives the oxazole proton signal in $CF_3{\cdot}CO_2H$ is only in accord with its location at C-5′.

EXPERIMENTAL

Unless otherwise stated, compounds (1)—(6) were prepared by heating the corresponding steroid (2 g) dissolved in methanolic 3.2% ammonia (100 ml) (from aqueous 32% ammonia) with cyanamide (2 mol. equiv.; Fluka; stabilised with 2% boric acid), at 40—45 °C for *ca.* 1 h, under nitrogen with stirring. Products were obtained by concentration under a reduced pressure and were washed with cold methanol and ether. I.r. spectra ($CHCl_3$ solutions) were recorded with a Perkin-Elmer 457 spectrometer (1 mm cells). Compounds (4) and (5) are not very soluble in chloroform; hence the frequencies of amino-group stretching and of the less intense nuclear mode were not very accurately determined. Absorptions due to the steroidal nucleus occurred at the expected values.[7,12] $[\alpha]_D$ Values (dioxan) were measured with a Perkin-Elmer 141 Polarimeter. ^{1}H N.m.r. spectra were recorded with a Hitachi–Perkin-Elmer R-20B apparatus. T.l.c. was carried out on Merck silica gel 60 F_{254} (0.25 mm thick) in chloroform–methanol (3 : 1 v/v); compounds (6) and (7) were revealed by spraying with 1% ethanolic 2,6-dichlorobenzoquinone *N*-chloroimide.

17β-(2-*Amino-oxazol-4-yl*)*androst-4-en-3-one* (1).— The solution obtained from reaction of cortexone was left overnight at *ca.* 5 °C. The *product* was obtained by evaporation (1.09 g, 50.8%) and recrystallised from ethanol–water (1 : 2); m.p. 259—261° (decomp.), $[\alpha]_D$ 122° (*c* 0.24) (Found: C, 74.35; H, 8.75; N, 7.9. $C_{22}H_{30}N_2O_2$ requires C, 74.55; H, 8.55; N, 7.9%); $\nu_{max.}$ 3 508 and 3 413 (NH_2 str.), and 1 640, 1 601, and 1 572 cm^{-1} (NH_2 scissor and ω).

17β-(2-*Amino-oxazol-4-yl*)-17α-*hydroxyandrost-4-ene-3,11-dione* (2).—From cortisone we obtained 1 g (46.9%) of crude product; a sample was purified by dissolving it in boiling absolute ethanol, under nitrogen, and collecting the *precipitate* formed on concentration under diminished pressure; m.p. 312—315° (decomp.), $[\alpha]_D$ 161° (*c* 0.16) (Found: C, 68.7; H, 7.15; N, 7.4. $C_{22}H_{28}N_2O_4$ requires C, 68.75; H, 7.35; N, 7.3%); $\nu_{max.}$ 3 512 and 3 417 (NH_2 str.), and 1 644, 1 604, and 1 572 cm^{-1} (NH_2 scissor and ω).

17β-(2-*Amino-oxazol-4-yl*)-11β,17α-*dihydroxyandrost-4-en-3-one* (3).—The solution obtained from reaction of cortisol (30 min) was evaporated to dryness and the solid was treated with cold methanol and washed with ether to give a pale yellow powder (1.115 g, 52.3%). A sample purified as for (2) gave a *solid*, m.p. 289—291° (decomp.), $[\alpha]_D$ 107° (*c* 0.11) (Found: C, 68.05; H, 8.0; N, 7.0. $C_{22}H_{30}N_2O_4$ requires C, 68.35; H, 7.8; N, 7.25%); $\nu_{max.}$ 3 510 and 3 415 (NH_2str.), and 1 645, 1 605, 1 573 cm^{-1} (NH_2 scissor and ω).

17β-(2-*Amino-oxazol-4-yl*)-17α-*hydroxyandrosta-1,4-diene-3,11-dione* (4).—From reaction of prednisone, at 45—47 °C, we collected a crystalline *product* (0.768 g, 36%), m.p. 308—311° (decomp.) (from absolute ethanol), $[\alpha]_D$ 147° (*c* 0.11) (Found: C, 69.0; H, 7.0; N, 7.15. $C_{22}H_{26}N_2O_4$ requires C, 69.1; H, 6.85; N, 7.3%); $\nu_{max.}$ *ca.* 3 500 and 3 400 (NH_2 str.), and 1 645, 1 602, and *ca.* 1 570 cm^{-1} (NH_2 scissor and ω).

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17β-(2-*Amino-oxazol-4-yl*)-11β,17α-*dihydroxyandrosta*-1,4-*dien*-3-*one* (5).—From reaction of prednisolone, after 3 h, we collected a pale yellow crystalline *product* (1.1 g, 51.5%), m.p. 271—272° (decomp.) (from absolute ethanol) $[\alpha]_D$ 74° (*c* 0.18) (Found: C, 68.95; H, 7.5; N, 7.25. $C_{22}H_{28}N_2O_4$ requires C, 68.75; H, 7.35; N, 7.3%); $\nu_{max.}$ *ca.* 3 500 and 3 400 (NH_2 str.), and 1 644, 1 604, and *ca.* 1 570 cm^{-1} (NH_2 scissor and ω).

17β-(2-*Amino-oxazol-4-yl*)-3,3-*ethylenedioxy*-17α-*hydroxy-androst*-5-*en*-11-*one* (6).—From reaction of cortisone 3-ethylene acetal,[13] at 47—49°, evaporation to dryness left a residue which was extracted with tetrahydrofuran (distilled from sodium), and 3 volumes of petroleum (b.p. 40—70°) were added causing a yellow oil to separate. This procedure was repeated (total *ca.* 150 ml of tetrahydrofuran) and the residual oil was discarded. The clear solution was evaporated to yield a pale yellow *solid* (1.61 g, 76%), giving needles (from ethanol), m.p. 224—226° (decomp.), $[\alpha]_D$ −14° (*c* 0.67) (Found: C, 67.1; H, 7.6; N, 6.5. $C_{24}H_{32}N_2O_5$ requires C, 67.25; H, 7.55; N, 6.55%); $\nu_{max.}$ 3 510 and 3 418 (NH_2 str.), and 1 643, 1 603, and 1 571 cm^{-1} (NH_2 scissor and ω).

2-*Amino*-4-*methyloxazole* (7).—To an aqueous solution (50%) of hydroxyacetone (6 g, 5.6 ml; 40.5 mmol) in methanol (400 ml) were added 32% ammonia (40 ml) and cyanamide (3.40 g, 81 mmol). The solution was kept for 3 h at 33—38 °C then for 1 h at room temperature. Evaporation *in vacuum* to *ca.* 30 ml was followed by extraction with methylene chloride (200 ml). The extract was washed twice with water, dried (Na_2SO_4), and evaporated to leave a pale yellow oil that crystallised at 20 °C (1.7 g, 42.8%). The *product* was collected as a solid condensing in a sublimator cooled at 0 °C (0.05 mmHg); resublimation yielded colourless crystals, m.p. 28—29° (under nitrogen) (Found: C, 48.65; H, 6.2; N, 28.3. $C_4H_6N_2O$ requires C, 48.95; H, 6.15; N, 28.55%); $\nu_{max.}$ 3 510 and 3 415 (NH_2 str.), and 1 643, 1 615, and 1 574 cm^{-1} (NH_2 scissor and ω). A sample prepared by the method of Crank [4] was identical (analytical and spectroscopic properties).

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