Tetrahedron. Vol. 31, pp. 1325 to 1330. Pergamon Press 1975. Printed in Great Britain

FUNCTIONALIZED ENAMINES—XXII[1]

ANNELATION OF ENAMINES OF POLYCYCLIC α,β-UNSATURATED KETONES; A FACILE PARTIAL SYNTHESIS OF FURANO- INDOLO- AND BENZSTEROIDS. TOTAL SYNTHESIS OF 3-OXA-A-NORSTEROID.

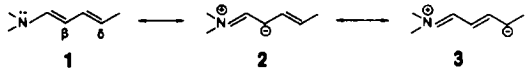
M. S. MANHAS* and J. W. BROWN[2a]
Stevens Institute of Technology, Hoboken, New Jersey, USA

U. K. PANDIT* and P. HOUDEWIND[2b]
Organic Chemistry Laboratory, University of Amsterdam, Nieuwe Achtergracht 129, Amsterdam, The Netherlands

(*Received in the UK 29 November 1974; Accepted for publication 31 December 1974*)

Abstract—Reaction of dienamine **4a** with substituted phenacyl bromides gave steroidal[3,4-*b*] furans **5a–g**. The same principle reaction was utilized for the total synthesis of (±) 2 - (*p* - chlorophenyl) - 3 - oxa - A - nor - estra - 1,5(10), 9(11) - triene - 17 - acetate **12a**. Treatment of **4a, b** with benzenediazonium salts, in DMF, followed by a Fischer-indole cyclization yielded steroidal[6,7-*b*] indoles **8a–k**. Dienamine **4b** could be annelated to benz[4,5,6] steroids **9a** and **9b** by reaction with methyl vinyl ketone and crotonaldehyde, respectively.

Dienamines (**1**→**2**→**3**) are ambident nucleophiles[3] which can undergo electrophilic attack at the nitrogen, the β- or the δ-carbon atom. Protonation of steroidal $\Delta^{3,5}$-



1 **2** **3**

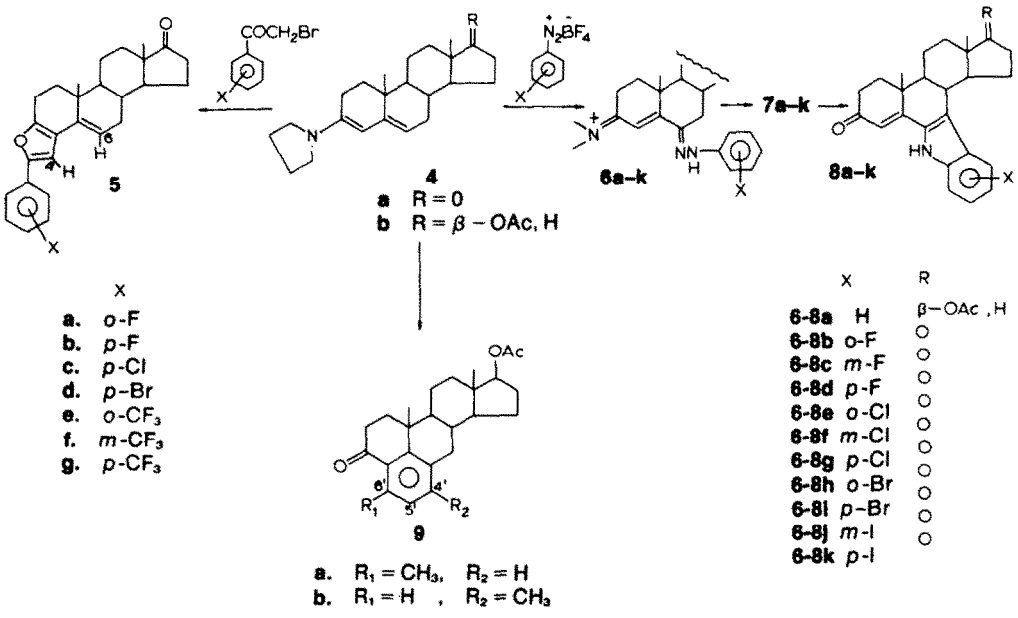
dienamines[4] has been suggested to involve addition to C-4 or C-6 under conditions of kinetic or thermodynamic control, respectively. In aliphatic dienamines, initial N-protonation is followed by migration of the proton, via the β-, to the δ-carbon atom.[5] Reaction of dienamines with electrophilic reagents displays, in general, a reactivity pattern which, besides varying with the nature of the electrophile,[6a–k] depends notably upon the temperature,[7] solvent [6a,7] and the base utilized for preparing the dienamine.[8a,b] In view of this fact dienamine-reagents can be harnessed for synthetic objectives by a judicious choice of the reaction parameters. This communication describes convenient syntheses of steroido[3,4-*b*]furans, steroido[6,7-*b*]indoles and benz[4,5,6]steroids by the annelation reaction of dienamines derived from Δ^4-3-keto steroids. In addition, using the same principle, the total synthesis of a 3-oxa-A-norestrane derivative has been achieved. This synthetic approach constitutes a viable alternative to procedures described in the literature, since the necessity of preparing complex synthons is eliminated.

Steroido[3,4-b]*furans.* Oxa-steroids derive considerable interest from the fact that several alkaloids, terpenoids and steroids incorporate a condensed furan moiety. Moreover, a few oxa-steroids have been reported to possess endocrine properties.[9,10] The partial synthesis of tetrahydro-furano,[11,14] dihydrofurano-[15] and furano steroids[16,17] have been accomplished through elaborate reaction sequences. The potentiality of utilizing the reaction of α-haloketones with enamines of cyclic α,β-unsaturated ketones, in the synthesis of condensed furan derivatives, in a one pot reaction, has recently been demonstrated in one of our laboratories.[18]

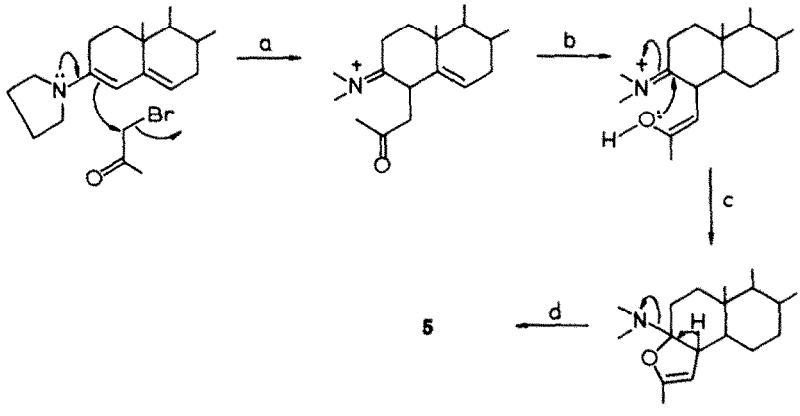
For synthesis of steroidofurans of type **5**, Δ^4-androstene-3,17-dione was readily converted to the corresponding $\Delta^{3,5}$-dienamine **4a**[19] in nearly quantitative yield. Treatment of **4a** with a series of ring substituted α-bromoacetophenones, in refluxing DMF, yielded furanosteroids **5a–g** in yields ranging from 4 to 30%, depending upon the nature and position of the substituent on the benzene ring (Table 1). The yield is significantly reduced when the bulky trifluoromethyl group is located in the ortho position to the bromoacetyl side chain. Reaction of **4a** with 1,1,1-trifluoro-3-bromo-2-propanone failed to give the expected furan system. The structures of the products were established by spectroscopic and analytical data. The IR spectra of **5a–g** showed the presence of a carbonyl absorption at 1742 cm^{-1} characteristic of the cyclopentanone system. The UV spectra of these compounds showed absorptions at 226 ± 2 (ε 7,300–15,000), sh 237 ± 2 (ε 8,800–15,600) and 314 ± 4 nm (ε 11,600–16,400), typical of conjugated furans.[20] The appropriate molecular ion was observed in the mass spectrum, in each instance, along with the M-15 fragment from a steroid nucleus. The appearance of two low field protons in the NMR spectra afforded additional evidence for the formation of the respective furanosteroids. Table 1 lists the chemical shifts of the furans. As expected, the C-4′ vinylic proton appeared as a singlet at δ 6·5–6·7 and C-6 proton as a triplet at δ 5·65–5·7. An exception to this pattern was the spectrum of **5a**, where, due to long range proton-fluorine coupling, the signal centered at δ 6·8 appeared as a doublet, J = 2 Hz. Another anomalous feature was observed in the NMR spectrum of **5b**. The chemical shift for the C-4′ proton is at δ 6·49 which is considerably more shielded than that observed for the other furans.

The formation of the furanosteroids **5a–g** may be rationalized in terms of nucleophilic attack on the haloketone at the carbon atom bearing bromine (step a), followed by nucleophile attack by the enolized ketone on the iminium function (step c). Finally loss of pyrrolidine results in the formation of the furan **5** (Scheme 2).[18]

Steroido[6,7-b]*indoles.* The indole moiety is a notable structural feature of a large number of alkaloids and



Scheme 1.



Scheme 2.

Table 1. 17 - Keto - 5' - (halophenyl) - Δ^5 - androstano[3,4-*b*]furans and 17 - keto - 5' - trifluromethylphenyl) - Δ^5 - androstano[3,4-*b*]furan

Compound	m.p. °C	% yield	Chemical shift, δ				
			3H, C-18	3H, C-19	1H, C-6	1H, C-4'	Ar
5a	271–74	30	0·88(s)	1·00(s)	5·70(m)	6·80(d)	6·9–7·6(m)
5b	256–57	17	0·90(s)	1·06(s)	5·65(m)	6·49(s)	6·75–7·7(m) A_2B_2
5c	255–56	27	0·90(s)	1·01(s)	5·75(m)	6·67(s)	7·2–8·7(m) A_2B_2
5d	278–80	26	0·91(s)	1·03(s)	5·75(m)	6·70(s)	7·5(m)
5e	190–91	3·9	0·89(s)	1·03(s)	5·65(m)	6·62(s)	7·2–7·84(m)
5f	161–63	14·6	0·85(s)	0·99(s)	5·69(m)	6·62(s)	7·2–7·84(m)
5g	173–75	16·9	0·92(s)	1·02(s)	5·73(m)	6·72(s)	7·4–7·80(m)

synthetic physiologically active compounds. This fact has prompted the synthesis of a number of indolo-steroids, in particular, those belonging to the [3,2-*b*]indolo and [3,4-*b*]indolo category.[21a-1] We therefore directed our attention to the general synthesis of steroido[6,7-b]indoles. Consistent with the observation[6a] that diazonium salts react at the δ-carbon of dienamines when DMF is used as solvent, treatment of **4b**[24] with benzenediazonium fluorborate or of **4a** with a series of halobenzenediazonium fluoborates, in dry DMF, at −45°, let to the formation of hydrazones **6a–k** (Scheme 1). Their NMR spectra are reported in Table 2. The hydrazones were treated, without purification, with $POCl_3$ to yield the cyclization products **7a–k**,[22] which underwent smooth hydrolysis in 2% methanolic sodium hydroxide to indole derivatives **8a–k**. The structures of

Table 2. NMR spectra of hydrazones 6

Compound	m.p. °C	% yield	Chemical shift, δ				
			3H, C-18	3H, C-19	$-CH_2-N$	Aromatic and vinylic protons	NH
6a	244–45	93	0·81(s)	1·11(s)			10·21
6b	240–42	30	0·88(s)	1·14(s)	3·95(m)	6·90–7·90	10·25
6c	265–67(dec)	37	0·87(s)	1·13(s)	3·95(m)	6·90–7·90	10·10
6d	284–86	56	0·86(s)	1·10(s)	3·95(m)	6·90–7·80	10·30
6e	202–202	38	0·86(s)	1·04(s)	4·01(m)	7·00–7·90	9·40
6f	250–53	33	0·89(s)	1·13(s)	3·93(m)	6·90–7·50	10·31
6g	304–306	74	0·85(s)	1·09(s)	3·92(m)	7·00–7·50	10·00
6h	272	26	0·86(s)	1·04(s)	4·01(m)	6·90–7·90	9·40
6i	315	57	0·88(s)	1·15(s)	3·95(m)	6·90–7·60	10·20
6j	308	46	0·87(s)	1·13(s)	3·98(m)	6·90–7·90	10·28
6k	312–14	35	0·87(s)	1·13(s)	3·95(m)	7·00–7·90	10·30

the indolosteroids were determined by their spectroanalytical data. The presence of bands at 3279 (N-H stretch), 1742 (carbonyl in a five-membered ring) and 1639 cm^{-1} (unsaturated ketone) in the IR spectra constituted strong evidence for indoles **8a–k**. Additional evidence for these structures was derived from the MS analysis. In each instance the correct molecular ion was observed. The formation of **7a–k** from hydrazones **6a–k** essentially represents a Fisher-indole synthesis and presumably follows the accepted mechanism for the latter cyclization.[22]

Benz[4,5,6]*steroids.* Although several reports[23a-d] describe annelation of steroids involving attachment of an aromatic ring across the C-4, C-5 and C-6 bonds, all of these require elaborate synthetic operations. The steroidal dienamine **4b** could be conveniently annelated to benzsteroids **9a** and **9b** by reacting it with vinyl methyl ketone and crotonaldehyde, respectively. The structure of the products followed from their spectral data. A salient point in distinguishing between isomers **9a** and **9b** was the difference in chemical shifts of the C-6′ CH_3 (at δ 2·51) in **9a**, and the C-4′ CH_3 (at δ 2·23) in **9b**. The observed paramagnetic shift in **9a** is consistent with the proximity of the methyl to the carbonyl function at C-3. The mechanism of formation of the benzsteroids has been discussed in an earlier communication.[24]

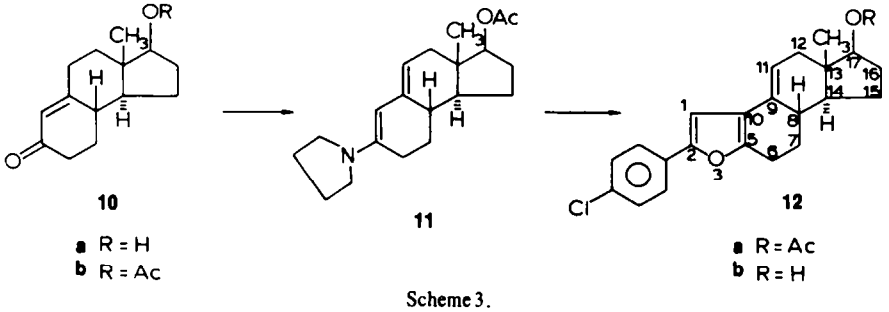
3-Oxa-A-NorSteroid. The reaction of α-haloketone with dienamine,[18] leading to furan formation, was utilized for the total synthesis of (±)2 - (*p* - chlorophenyl) - 3 - oxa - A - nor - estra - 1,5(10), 9(11)-triene-17-acetate **12a** (Scheme 3). The key intermediate for this synthesis was ketol **10a**, which has been described previously by several workers.[25a-d] The ketol was acetylated **10b**[26] and the latter converted into the corresponding dienamine **11**. Reaction of **11** with *p*-chlorophenacyl bromide in DMF yielded crystalline **12a**, m.p. 148–50° in 20% yield. The presence of three significant downfield protons at δ 4·68 H, C-17 5·55 H, C-11 and 6·52 H, C-1 attested to the structure of **12a**. An attempt to introduce a hydroxy group at C-11 by treatment of **12a** with $LiAlH_4$-BF_3-etherate resulted in deacetylation **12b** of the starting compound.

EXPERIMENTAL

M.ps were determined on a Mel-Tamp apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 247 Grating and Unicam SP200 Spectrometers. NMR spectra in $CDCl_3$ solutions containing TMS as an internal standard were recorded on Varian A-60A and A-60D spectrometers; chemical shifts are reported in δ units (ppm downfield from TMS). Mass spectra were obtained with a Hitachi RMU-7 spectrometer. Elemental analyses were performed by Bernhardt, Max-Planck Institute, Mülheim, West Germany and Mr. H. Pieters, Organic Chemistry Laboratory, University of Amsterdam.

Preparation of Steroido[3,4-*b*]*furans* **5**. The general method consists of stirring a mixture of one equivalent of dienamine **4a** with one equivalent of substituted phenacyl bromide in dry DMF (35 ml) under N_2, at 150° for 18 h. Water was subsequently added, the mixture warmed on a steam bath for 1 h, the solvent evaporated and the residue extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried and the product obtained upon removal of the solvent chromatographed by preparative layer chromatography (PLC). Elution with EtOAc, filtration through Celite, and evaporation of the solvent gave a product which, after recrystallisation from MeOH, resulted in pure **5**. Specific examples of furanosteroid preparation and their properties are presented here.

5′ - (m - Trifluoromethylphenyl) - Δ⁵ - androstano - [3,4-b]furan - 12 - one **5f**. A mixture of dienamine **4a** (2 mmol) and α - bromo - m - trifluoromethylacetophenone (2 mmol) in 35 ml of dry DMF was stirred under N_2 at 150°, for 18 h. The reaction mixture was worked up according to the general procedure. Recrystallisation of the product from MeOH, resulted in pure **5f**, m.p. 161–163°; yield 134 mg (14·6%); IR (Nujol) 1742 cm^{-1} (cyclopentanone



Scheme 3.

carbonyl); NMR δ 0·85 (s, 3H, C-18), 0·99 (s, 3H, C-19), 5·69 (m, 1H, C-6), 6·62 (s, 1H, C-4), 7·2–7·84 (m, 4H, ArH); mass spectrum, M+ at *m/e* 454 (MW calc. for $C_{28}H_{29}O_2F_3$) Found: C, 74·00; H, 6·45. Calc. for $C_{28}H_{29}O_2F_3$: C, 74·03; H, 6·38%).

5' - (o - Fluorophenyl) - Δ³ - androstano[3,4-b]furan - 17 - one **5a**. Recrystallisation of the appropriate PLC fraction from MeOH, resulted in pure **5a**, m.p. 271–72°; yield 172,4 mg (30%) UV λ_{max} (MeOH) 225 (12,200), sh 237 (11,380) and 310 nm (11,600); IR (Nujol) 1742 cm^{-1} (cyclopentanone carbonyl); NMR δ 0·88 (s, 3H, C-18), 5·7 (m, 1H, C-6), 6·8 (d, 1H, C-4 J = 2 Hz), 6·9–7·6 (m, 4H, ArH); mass spectrum, M+ at *m/e* 404. (MW calc. for $C_{28}H_{29}O_2F$) (Found: C, 80·10; H, 7·10. Calc. for $C_{28}H_{29}O_2F$: C, 80·25; H, 7·16%).

5' - (p - Fluorophenyl) - Δ² - androstano[3,4-b]furan - 17 - one **5b**. Recrystallisation of the appropriate PLC fraction from MeOH, resulted in pure **5b**, m.p. 255–56°; yield 154 mg (17%); IR (Nujol) 1742 cm^{-1} (cyclopentanone carbonyl); NMR 0·90 (s, 3H, C-18), 1·06 (s, 3H, C-19); 5·65 (m, 1H, C-6), 6·49 (s, 1H, C-4); 6·75–7·7 (m, 4H, ArH); mass spectrum, M+ at *m/e* 404 (MW calc. for $C_{28}H_{29}O_2F$) (Found: C, 80·00; H, 7·20. Calc. for $C_{28}H_{29}O_2F$: C, 80·25; H, 7·16%).

5' - (p - Chlorophenyl) - Δ³ - androstano[3,4-b]furan - 17 - one **5c**. M.p. 255–56°; yield 156 mg (27%); IR (Nujol) 1742 cm^{-1} (cyclopentanone carbonyl); NMR δ 0·90 (s, 3H, C-18), 6·67 (s, 1H, C-4'), 7·2–8·7 (m, 4H, ArH); UV λ_{max} (MeOH) 228 (11,300), sh 237 (11,100), and 315 nm (13,500); mass spectrum, M+ at *m/e* 420 (MW calc. for $C_{27}H_{29}O_2Cl$) (Found: C, 76·80; H, 7·02. Calc. for $C_{27}H_{29}O_2Cl$: C, 77·09; H, 6·89%).

5' - (p - Bromophenyl) - Δ³ - androstano[3,4-b]furan - 17 - one **5d**. Recrystallisation of the appropriate PLC fraction from MeOH, resulted in pure **5d**, m.p. 278–80°; yield 241 mg (26%); IR (Nujol) 1742 cm^{-1} (cyclopentanone carbonyl); NMR δ 0·91 (s, 3H, C-18), 1·03 (s, 3H, C-19), 5·75 (m, 1H, C-6), 6·70 (s, 1H, C-4), 7·5 (s, 4H, ArH); UV λ_{max} (MeOH) 224 (7,300), sh 235 (8,800), and 316 nm (12,700); mass spectrum, M+ at *m/e* 465 (MW calc. for $C_{27}H_{29}O_2Br$.) (Found: C, 69·70; H, 6·64. Calc. for $C_{27}H_{29}O_2Br$: C, 69·71; H, 6·23%).

5' - (o - Trifluoromethylphenyl) - Δ³ - androstano[3,4-b]furan - 17 - one **5e**. Recrystallisation of the appropriate PLC fraction from MeOH, resulted in pure **5e**, m.p. 190–92°; yield 36 mg (3·9%); IR (Nujol) 1742 cm^{-1} (cyclopentanone carbonyl); NMR δ 0·89 (s, 1H, C-6), 6·62 (s, 1H, C-4'), 7·2–7·84 (m, ArH); UV λ_{max} (MeOH) 228 (15,000), sh 239 (15,600), and 318 nm (12,300); mass spectrum, M+ at *m/e* 454 (MW calc. for $C_{28}H_{29}O_2F_3$) (Found: C, 74·00; H, 6·45. Calc. for $C_{28}H_{29}O_2F_3$: C, 74·03; H, 6·38).

5' - (p - Trifluoromethylphenyl) - Δ³ - androstano[3,4-b]furan - 17 - one **5g**. Recrystallisation of the appropriate PLC fraction from MeOH, resulted in pure **5g**, m.p. 174–75°; yield 154 mg (16·9%); IR (Nujol) 1742 cm^{-1} (cyclopentanone carbonyl); NMR δ 0·92 (s, 3H, C-18), 1·02 (s, 3H, C-19), 5·73 (m, 1H, C-6), 6·72 (s, 1H, C-4'), 7·4–7·80 (m, 4H, ArH); UV λ_{max} (MeOH) 225 (14,350) and 317 nm (16,400); mass spectrum, M+ at *m/e* 454 (MW calc. for $C_{28}H_{29}O_2F_3$) (Found: C, 74·00; H, 6·35. Calc. for $C_{28}H_{29}O_2F_3$: C, 74·03; H, 6·38%).

Preparation of 17 - keto - Δ³ - androstan - 6(halophenyl)hydrazone - 3 - pyrrolidinium tetrafluoroborate **6**. *General Method.* To a solution of 2 mmol of dienamine **4a, b** in 80 ml of DMF, cooled under nitrogen to −45°, 3 mmol of benzenediazonium fluoroborate dissolved in 20 ml of DMF, was added in 0·5 h and the mixture allowed to reach room temperature. Evaporation of the solvent afforded, after recrystallisation from MeOH, the pure salt **6a–k**. The physical and spectral properties of the hydrazones are presented in Table 1.

17β - Acetoxy- and 17 - keto - Δ⁴ - androstano[6,7-b]indole **8**. In the general procedure, a solution consisting of 1 mmol of **6** in 35 ml of $POCl_3$ was stirred for 64 h at room temperature. The green-fluorescent mixture was poured into water, with cooling, and neutralized with $NaHCO_3$ solution. The precipitate was dissolved in CH_2Cl_2 and dried. Following the removal of solvent, the indole salt **7** was obtained: IR (Nujol) 3390 cm^{-1} (NH); NMR δ 3·90–4·40 (m, CH_2–N). The crude indole salt **7** was suspended in 15 ml of methanol and treated with 4 ml of 2% NaOH. After stirring for 1 h, the solution was neutralized and the precipitate removed by filtration. The precipitate was dissolved in methylene chloride, washed with water, and dried. The solvent was removed in vacuo and the residue recrystallised to afford indole **8**.

17β - Acetoxy - Δ⁴ - androstano[6,7-b]indole **8a**. Hydrolysis of the salt **7a** was followed by acetylation with Ac_2O, whereupon crystalline **8a** was obtained. Recrystallisation from C_6H_6 yielded 250 mg (60%) of pure **8a**, m.p. 350–355° dec., IR (KBr) 3400 (NH), 1725 (OAc), 1640 cm^{-1} (conjugated ketone); NMR($CDCl_3$) δ 1·05, 1·07 (2 × s, 3H, C-18 and 3H, C-19), 2·05 (s, $COOCH_3$), 4·63 (t, 1H, C-17, J = 8), 6·39 (s, 1H, C-4), 6·9–7·8 (m, ArH); UV(EtOH) λ_{max} 217 (26,000), 262 (9,200), 370 (25,800) (Found: C, 77·6; H, 7·40; N, 3·40. Calc. for $C_{27}H_{31}NO_3$: C, 77·66; H, 7·48; N, 3·35%).

17 - Keto - Δ⁴ - androstano[6,7-b] - 3' - fluorindole **8b**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8b**, m.p. 345°; yield 55 mg (22%); IR (Nujol) 3279 (NH), 1742 (cyclopentanone carbonyl) 1639 cm^{-1} (conjugated ketone); NMR δ 1·10 (s, 3H, C-18), 1·16 (s, 3H, C-19), 6·38 (s, 1H, C-4), 6·80–8·10 (m, ArH); mass spectrum, M+ at *m/e* 391 (MW calc. for $C_{25}H_{26}O_2NF$) (Found: C, 76·81; H, 6·70; N, 3·46. Calc. for $C_{25}H_{26}O_2NF$: C, 76·67; H, 6·64; N, 3·57%).

17 - Keto - Δ⁴ - androstano[6,7-b] - 4' - fluoroindole **8c**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8c**, m.p. 350°; yield 134·5 mg (47%); IR (Nujol) 3279 (NH), 1742 (cyclopentanone carbonyl), 1639 cm^{-1} (conjugated ketone); NMR δ 1·00 (s, 3H, C-18), 1·05 (s, 3H, C-19), 6·32 (s, 1H, C-4), 6·40–8·00 (ArH); mass spectrum, M+ at *m/e* 391 (MW calc. for $C_{25}H_{26}O_2NF$).

17 - Keto - Δ⁴ - androstano[6,7-b] - 5' - fluoroindole **8d**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8d**, m.p. 350°; yield 135 mg (39%); IR (Nujol) 3279 (NH), 1742 (cyclopentanone carbonyl), 1639 cm^{-1} (conjugated ketone); NMR δ 1·02 (s, 3H, C-18), 1·08 (s, 3H, C-19), 6·38 (s, 1H, C-4), 6·90–7·70 (ArH); mass spectrum, M+ at *m/e* 391 (MW calc. for $C_{25}H_{26}O_2NF$) (Found: C, 76·51; H, 6·70; H, 3·62. Calc. for $C_{25}H_{26}O_2NF$: C, 76·67; H, 6·64; N, 3·57%).

17 - Keto - Δ⁴ - androstano[6,7-b] - 3' - chloroindole **8e**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8e**, m.p. 350° yield 65 mg (18%); IR (Nujol) 3279 (cyclopentanone carbonyl), 1639 cm^{-1} (conjugated carbonyl); NMR δ 1·02 (s, 3H, C-18), 1·09 (s, 3H, C-19), 6·77 (s, 1H, C-4), 7·00–8·00 (m, ArH), 1630 (NH); mass spectrum, M+ at *m/e* 407 (MW calc. for $C_{25}H_{26}O_2NCl$) (Found: C, 73·60; H, 6·58; N, 3·31. Calc. for $C_{25}H_{26}O_2NCl$: C, 73·58; H, 6·38; N, 3·43%).

17 - Keto - Δ⁴ - androstano[6,7-b] - 4' - chloroindole **8f**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8f**, m.p. 350°; yield 61 mg (18·8%); IR (Nujol) 3279 (cyclopentanone carbonyl), 1639 cm^{-1} (conjugated carbonyl); NMR δ 1·01 (s, 3H, C-18), 1·05 (s, 3H, C-19), 6·20 (s, 1H, C-4), 6·90–7·63 (ArH); mass spectrum, M+ at *m/e* 407 (MW calc. for $C_{25}H_{26}O_2NCl$) (Found: C, 73·60; H, 6·41; N, 3·48. Calc. for $C_{25}H_{26}O_2NCl$: C, 73·58; H, 6·41; N, 3·43%).

17 - Keto - Δ⁴ - androstano[6,7-b] - 5' - chloroindole **8g**. Recrystallisation from methylene chloride-methanol resulted in pure **8g**, m.p. 300°; yield 183 mg, (42%), IR (Nujol) 3279 (NH), 1742 (cyclopentanone carbonyl), 1639 cm^{-1} (conjugated carbonyl); NMR δ 1·04 (s, 3H, C-18), 1·12 (s, 3H, C-19), 6·34 (s, 1H, C-4), 7·10–8·00 (ArH); mass spectrum, M+ at *m/e* 407 (MW calc. for $C_{25}H_{26}O_2NCl$) (Found: C, 73·71; H, 6·58; N, 3·31. Calc. for $C_{25}H_{26}O_2NCl$: C, 73·58; H, 6·38; N, 3·43%).

17 - Keto - Δ⁴ - androstano[6,7-b] - 3' - bromoindole **8h**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8h**, m.p. 350°; yield 43 mg (12·5%); IR (Nujol) 3279 (NH), 1742 (cyclopentanone carbonyl), 1639 cm^{-1} (unsaturated ketone); NMR δ 1·03 (s, 3H, C-19), 6·82 (s, 1H, C-4), 7·80–8·00 (ArH); mass spectrum, M+ at *m/e* 452 (MW calc. for $C_{25}H_{26}O_2NBr$) (Found; C, 66·55; H, 5·87; N, 3·25. Calc. for $C_{25}H_{26}O_2NBr$: C, 66·34; H, 5·75; N, 3·03%).

17 - Keto - Δ⁴ - androstano[6,7-b] - 5' - bromoindole **8i**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8i**, m.p. 350°; yield 116 mg (25%), IR (Nujol) 3279 (NH), 1742 (cyclopentanone carbonyl); 1639 cm^{-1} (unsaturated carbonyl); NMR δ 1·04 (s, 3H, C-18), 1·09 (s, 3H, C-19), 6·39 (s, 1H, C-4), 7·33 (s, ArH), 7·94 (NH), mass spectrum, M+ at *m/e* 452 (MW calc. for

$C_{25}H_{26}O_2NBr$) (Found: C, 66·26; H, 5·80; N, 2·90. Calc. for $C_{25}H_{26}O_2NBr$: C, 66·34; H, 5·75; N, 3·30%).

17 - *Keto* - Δ^4 - *androstano*[6,7-b] - 4' - *iodoindole* **8j**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8j**, m.p. 312–14°; yield 198 mg, (41·5%), IR (Nujol) 3279 (NH), 1742 (cyclopentanone carbonyl); 1639 cm^{-1} (conjugated carbonyl); NMR δ 1·02 (s, 3H, C-18), 1·07 (S, 3H, C-19), 6·37 (s, 1H, C-4), 7·20–7·70 (m, ArH), 11·45 (NH); mass spectrum, M+ at *m/e* 499 (MW calc. for $C_{25}H_{26}O_2NI$) (Found: C, 60·20; H, 5·50; N, 2·65. Calc. for $C_{25}H_{26}O_2NI$: C, 60·10; H, 5·20; N, 2·80%).

17 - *Keto* - Δ^4 - *androstano*[6,7-b] - 5' - *iodoindole* **8k**. Recrystallisation from CH_2Cl_2–MeOH resulted in pure **8k**, m.p. 312–14°; yield 228 mg, (50%), IR (Nujol) 3279 (NH); 1742 (cyclopentanone carbonyl), 1639 cm^{-1} (conjugated carbonyl); NMR δ 1·02 (s, 3H, C-18), 1·07 (s, 3H, C-19), 6·38 (s, 1H, C-4), 7·10–7·62 (m, ArH), 8·11 (NH); mass spectrum, M+ at *m/e* 499 (MW calc. for $C_{25}H_{26}O_2NI$) (Found: C, 60·10; H, 5·30; N, 2·75. Calc. for $C_{25}H_{26}O_2NI$: C, 60·10; H, 5·20; N, 2·80%).

Preparation of Benz[4,5,6]*Steroids* **9**. A mixture of one equivalent of **4b** and five Eqns of methyl vinyl ketone or crotonaldehyde, in 2 ml of toluene, was heated at 140° for 40–45 h. The reaction products were hydrolysed and the resulting oil chromatographed over a florisil column (eluent C_6H_6/EtOAc, 100:1). The pentacylic steroids **9a, b**, which were isolated along with the hydrolytic product corresponding to the dienamine **4b**, were recrystallised from benzene cyclohexene mixture.

17β - *Acetoxy* - 4' - *methylbenz*[4,5,6]*androst* - 4 - *ene* - 3 - *one* **9a**. M.p. 162–164°, yield 11%; IR (KBr) 1715 (ester C=O), 1670 cm^{-1} (C=C–C=O); NMR ($CDCl_3$) δ 0·88 (s, 3H, C-18), 1·21 (s, 3H, C-19), 2·05 (s, $COOCH_3$), 2·23 (s, 3H, C-4'), 4·61 (t, 1H, C-17, J = 7), 7·11 (d, 1H, C-5', J = 8), 7·81 (d, 1H, C-6', J = 8). UV(EtOH) λ_{max} 212(18,400), 263(12,000) (Found: C, 78·8; H, 8·6. Calc. for $C_{25}H_{32}O_3$: C, 78·91; H, 8·48%).

17β - *Acetoxy* - 6' - *methylbenz*[4,5,6]*androst* - 4 - *ene* - 3 - *one* **9b**. M.p. 160–162°, yield 15%; IR(KBr) 1730 (ester C=O), 1670 cm^{-1} (C=C–C=O); NMR($CDCl_3$) δ 0·85 (s, 3H, C-18), 1·15 (s, 3H, C-19), 2·05 (s, $COOCH_3$), 2·51 (s, 3H, C-6'), 4·66 (t, 1H, C-17, J = 8·5), 6·98 and 7·04 (AB system, 1H, C-4' and 1H, C-5', J = 8); UV(EtOH) 213(20,700), 261(9,500) (Found: C, 78·8; H, 8·5. Calc. for $C_{25}H_{32}O_3$: C, 78·91; H, 8·48%).

dl - 17β - *Hydroxy* - Δ^9(10) - *des* - *A* - *androston* - 5 - *one* **10a** was prepared by the method of Chinn and Dryden.[25c]

dl - 17β - *Acetoxy* - Δ^9(10) - *des* - *A* - *androstan* - 5 - *one* **10b**. The ketol **10a** was acetylated overnight at room temperature with a 2:1 mixture of pyridine acetic anhydride. The solvent was removed *in vacuo* to afford 2·37 g of **10b** m.p. 78–80 [lit.[26] m.p. 81–82°]; NMR ($CDCl_3$) δ 0·85 (s, 3H, $-CH_3$), 2·07 (s, CH_3CO), 4·68 (t, 1H, C-17), 5·90 (s, 1H, vinylic proton); mass spectrum M+ at *m/e* 262 (MW calc. for $C_{16}H_{22}O_3$).

Preparation of the pyrrolidine enamine of dl - 17β - *acetoxy* - Δ^9(10) - *des* - *A* - *androsten* - 5 - *one* **11**. The ketoacetate **10b** 1·16 g (4·4 mmol), pyrrolidine, 0·62 g (8·8 mmol) and 50 ml of benzene were refluxed for 5·5 h using a Dean-Stark water separator. The solvent and excess pyrrolidine were removed under reduced pressure. The residue was washed with a small portion of ethyl ether-hexane, dried under high vacuum: yield 1·1 g (82%) of **11**; NMR ($CDCl_3$) δ: 0·36 (s, 3H, $-CH_3$), 3·18 (m, 4H, $-CH_2-N$), 4·55–5·15 (3H, C-10), C-11, 17αH).

dl - 2 - (p - *Chlorophenyl* - 3 - *oxa* - *A* - *norestra* - 1,5(10),9(11) - *trien* - 17β - *ol acetate* **12a**. A mixture consisting of the dienamine **11** (1·1 g, 3·8 mmol) and *p*-chlorophenacyl bromide (0·89 g, 3·85 mmol) in 45 ml of dry DMF was stirred for 18 h under nitrogen, at 150°. Water was subsequently added, the mixture warmed on a steam bath for 1 h, the solvent removed under diminished pressure and the residue extracted with CH_2Cl_2. The organic phase was washed with water, dried and the crude material obtained upon removal of the solvent, separated by preparative thin layer chromatography in a (2:3) hexane chloroform system. The fraction (R_f 0·6) 450 mg, was re-chromatographed and afforded **12a** on crystallisation from MeOH. The first fraction consisted of 88·7 mg (26%); m.p. 148–50°; IR (Nujol): 1724 cm^{-1} (ester carbonyl); λ_{max} (methanol): 227 (ϵ 10,250) and 316 nm (ϵ 12,500); NMR ($CDCl_3$), δ: 0·81 (s, 3H-CH_3), 1·98 (s, 3H, CH_3CO), 2·72 (m, allylic protons), 4·68 (m, 1H, C-17), 5·55 (m, 1H, C-11), 6·52 (s, 1H, C-1), 7·31 (m, 4H, A_2B_2, ArH); mass spectrum; M+ at *m/e* 396 (MW calc. for $C_{24}H_{25}O_3Cl$) (Found: C, 72·52; H, 6·55. Calc. for $C_{24}H_{25}O_3Cl$: C, 72·64; H, 6·30%).

Acknowledgement—Part of the work was carried out under auspices of the Netherlands Foundation for Chemical Research (SON) and with fininancial support from the Netherlands Organization for Advancement of Pure Research (ZWO).

REFERENCES

[1]Part XXI. M. S. Manhas, J. M. Brown and U. K. Pandit, *Heterocycles* in press.

[2a]Taken in part from the Ph.D. thesis of J. W. Brown, Stevens Institute of Technology, Hoboken, NJ, USA; [b]Taken in part from the doctorate thesis of P. Houdewind, University of Amsterdam.

[3]R. Gomper, *Angew. Chem. Internat. Edn. Engl.* **3**, 560 (1964).

[4]J. A. Marshall and W. S. Johnson, *J. Org. Chem.* **28**, 421 (1963).

[5]G. Optiz and W. Merz, *Ann.* **652**, 139, 158, 163 (1962).

[6]See for example: [a]J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, *J. Am. Chem. Soc.* **78**, 430 (1956); [b]G. Stork and G. Birnbaum, *Tetrahedron Letters* 313 (1961); [c]L. Velluz, G. Nominé, R. Bucourt, A. Pierdet and Ph. Dufay, *Ibid.* 127 (1961); [d]H. Evers, U. K. Pandit and H. O. Huisman, *Synth. Comm.* **1**, 89 (1971); [e]U. K. Pandit, K de Jonge, K. Erhart and H. O. Huisman, *Tetrahedron Letters* 1207 (1969); [f]N. F. Firrell and P. W. Hickmott, *J. Chem. Soc.* (C) 2320 (1968); [g]M. J. M. Pollmann, U. K. Pandit and H. O. Huisman, *Rec. Trav. Chim.* **89**, 929 (1970); [h]T. Watanabe and N. Soma, *Chem. Pharm. Bull.* **18**, 1604 (1970) A comprehensive discussion on the relationship between the electrophile and the reactivity pattern will be presented elsewhere.

[7]U. K. Pandit, W. A. Zwart Voorspuij and P. Houdewind, *Tetrahedron Letters* 1997 (1972).

[8a]P. Houdewind and U. K. Pandit, *Ibid.* 2359 (1974); [b]P. Houdewind, U. K. Pandit, A. K. Bose, R. J. Brambilla and G. L. Trainor, *Heterocycles* **1**, 53 (1973).

[9]R. Pappo and C. J. Jung, *Tetrahedron Letters* 365 (1962).

[10]S. D. Levine, *J. Med. Chem.* **8**, 537 (1965).

[11]L. Takes, In *Steroid Reactions* (Edited by C. Djerassi), p. 457. Holden Day, San Francisco, Calif. (1963).

[12]J. M. Erikson and D. L. Forbes, *Ibid.* p. 327.

[13]S. D. Levine, *Steroids* **15**, 209 (1970).

[14]M. Kishi and T. Komeno, *Tetrahedron* **27**, 1527 (1971).

[15]P. Hodge, J. A. Edwards and J. H. Fried, *Tetrahedron Letters* 5157 (1966).

[16]S. Julia and C. Moutonnier, *Bull. Soc. Chim.* 979 (1964).

[17]T. L. Popper, F. E. Carlon and O. Gnoj, *J. Chem. Soc.* (C), 1344 (1970).

[18]U. K. Pandit, H. R. Reus and K. de Jonge, *Rec. Trav. Chim.* **89**, 956 (1970).

[19]F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.* **75**, 1918 (1953).

[20]J. Szmuszkovicz, *Advances in Organic Chemistry* (Edited by R. A. Raphael, E. C. Taylor and H. Wijnberg), Vol. 4, p. 86. Wiley, NY (1963).

[21a]C. Dorée, *J. Chem. Soc.* 638 (1909); [b]C. Dorée and V. A. Petrow, *Ibid.* 1391 (1935); [c]W. Rossner, *Z. Physiol. Chem.* **249**, 267 (1937); [d]E. Schwenk and B. Whitman, *J. Am. Chem. Soc.* **59**, 949 (1937); [e]H. Antaki and V. Petrow, *J. Chem. Soc.* 901 (1951); [f]E. W. Warnhoff and P. Nanonggai, *J. Org. Chem.* **27**, 1186 (1962); [g]Y. Ban and Y. Sato, *Chem. Pharm. Bull. (Tokyo)* **13**, 1073 (1965); [h]J. Bukingham and R. D. Guthrie, *J. Chem. Soc.* (C), 3079 (1968); [i]N. J. Doorenbos and Mu Tsu Wu, *J. Med. Chem.* **11**, 158 (1968); [j]V. Carelli, P. Marchini, M. Cardellini and F. Michetti Moracci, *Ann. Chem. (Rome)* **59**, 163 (1969), *Chem. Abstracts* **71**, 22246 c (1971); [k]M. Akiba and S. Ohki, *Chem. Pharm. Bull. (Tokyo)* **18**, 2195 (1970); [l]D. J. Harvey and S. Reid, *Tetrahedron* **28**, 2489 (1972).

[22]B. Rolinson, *Chem. Rev.* **63**, 313 (1963).

[23a]J. M. H. Graves and H. J. Ringold, *Steroids Supp. I* **23** (1965); [b]R. Sciaky and U. Pallini, *Tetrahedron Letters* 1839 (1964); [c]R.

Gardi, R. Vitali and P. P. Castelli, *Ibid.* 3203 (1966); [d]T. Komeno, S. Ishihara, K. Takigawa, H. Itami and H. Iwakura, *Chem. Pharm. Bull. (Tokyo)* **17**, 2586 (1969).

[24]P. Houdewind, J. C. Lapierre Armande and U. K. Pandit, *Tetrahedron Letters* 591 (1974).

[25a]L. Velluz, G. Nominé, G. Amiard, N. Torelli and J. Cerede, *Compt. Rend.* **257**, 3086 (1963); [b]J. N. Gardnes, B. A. Anderson and E. P. Oliveto, *J. Org. Chem.* **34**, 107 (1969); [c]L. J. Chinn and H. L. Dryden, Jr., *Ibid.* **26**, 3904 (1961); [d]D. Lednicer and D. E. Emert, *Ibid.* **34**, 1151 (1969).

[26]J. Kurosawa, H. Shimojima and Y. Osawa, *Steroids Suppl. I* 185 (1965).