Tetrahedron Vol. 32, pp 79 to 88. Pergamon Press 1976 Printed in Great Britain

9(11)-SECOESTRA-11,17-DIOIC ACIDS AND RELATED COMPOUNDS

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(*Received in UK* 10 *June* 1975; *Accepted for publication* 31 *July* 1975)

Abstract—While hydrogenations of **2b** furnished a mixture in which the *rac* 14α isomer **8b** predominated, the *rac* lactone **6** was hydrogenolyzed to give the *rac* 14β diacid **9a**. Clemmensen reduction of **6** gave the *rac* 14α tetrahydro compound **7a**. Another route to **8** involved conversion of the *d*-ketoacid **11b** into **23b** via the cyanolactone **20b** or the amidolactone **21b**. Base-catalyzed elimination at 206° yielded the Δ^{16} diester **27** which was hydrogenated to **8c**. An analogous conversion was also carried out in the ring B reduced series **13**→**20a** + **21a**→**23a**→**25a**→**26**. In the 14β series, using the same sequence of reactions, the *rac* ketoacid **10a** was transformed into the *rac* lactone ester **29**. In distinction from the 14α series, treatment with alkali at 206° gave only partial elimination, the double bond migrating to the 14,15 position to furnish **2**. Evidence is presented that amides of the ketoacid **13a** exist in the hydroxylactam form **30** and can be readily O-alkylated to furnish **22**. Attempts to aromatize ring B of **13a** with DDQ led to lactones **15** and **16**, while reaction of the ester **13b** with DDQ gave the pentaene **17** and the hexaene **18**, establishing that dehydrogenation proceeded stepwise in the sequence Δ^{8}, Δ^{14} and finally Δ^{6}.

Several years ago we obtained[1] *rac* - 3 - methoxy - 14β - hydroxy - 9(11) - secoestra - 1,3,5(10),6,8 - pentaen - 11,17β - dioic acid dimethyl ester (**1b**) (Chart 1) and its dehydration product **2b** through condensation of 2 - methoxy - 6 - lithionaphthalene (**3**) with 2 - methyl - 2 - carboxymethyl - 3 - oxocyclopentanecarboxylic acid dimethyl ester (**4**)†. Independently Banerjee *et al.*[4] performed this condensation and carried on the resulting acid **2a** to the etioacid **5**. Our next aim was the preparation of the 14α- and 14β-dihydro derivatives **8** and **9** of **2b**; the different approaches taken are discussed in this paper.

Hydrogenation of **2b** furnished an oily intractable mixture of the 14α-dihydro compound **8b** and the epimeric 14β ester **9b** in the ratio 7:1, as judged from the respective C_{18} Me signals at 0·73 and 1·20 ppm.[5] Extensive experiments designed to separate them were unsuccessful. Hydrolysis of the mixture caused only partial purification of the acid **8a** and therefore other approaches were undertaken.

The acid **1a** was readily transformed into the lactone **6**, which must have the *cis* ring juncture. Reductive lactone ring-opening was carried out in two fashions: Clemmensen reaction afforded a mixture of the dicarboxylic acids **7a** and **7b**, the former predominating (C_{18} Me signals at 0·86 and 1·28 ppm[5]). Buchta and Ziener reported[6] a related lactone ring opening, with the preferential formation of that isomer in which the new C–H bond formed had the same configuration as the original C–O bond, in conformity with our present finding. On the other hand, the lactone **6** could be smoothly hydrogenolyzed to the diacid **9a** by virtue of the benzylic oxygen. The ester **9b** exhibited a chemical shift at 1·20 ppm, establishing the 14β configuration.[5]

†At the time of publication[1] we were unaware that the fragment **4** had been prepared not only by Stork,[2] but already a few years earlier by Banerjee and Das Gupta.[3] We apologize to Prof. Banerjee for this omission.

In connection with another synthesis of aromatic steroids[7] we required 11-ketoequilenin 3-methyl ether and its 14β epimer for direct comparison with one of our racemic products, and obtained them by cyclization of the ketoacids **11** and **10**, respectively. It was obvious that the last two compounds might serve also as starting materials for alternative routes to **8** and **9** by conversion of the carbonyl at position 17 into a carboxyl.

Three teams synthesized **11** and **10**: Horeau *et al.*[8] prepared the racemic acid **11a**; Brain *et al.*[5b] the racemic acids **11a** and **10a**; and Dygos and Chinn[9] made the optically active acid **11b** starting with the readily available[10,11] estradiol degradation product **12a** (Chart 2). Our own efforts, also starting with the acid **12a**, showed that of several variants used the experimental procedure of Dygos and Chinn gave the best results. Our other approaches were less successful: hydrolysis followed by Jones oxidation furnished the diketoacid **12b** which on catalytic hydrogenation yielded the ketoacid **13a**. This on treatment with 2–3 moles of DDQ gave a mixture of the two lactones **15** and **16**, the former characterized by UV absorption at 278 nm and the C_{18}Me shift at 1·13 ppm. The latter had the typical methoxynaphthalene UV absorption and the C_{18} Me signal at 0·92 ppm (deshielding by aromatic ring B). The use of less than 2 moles of DDQ had the effect of diminishing but never eliminating the amount of **16** produced, and with 5 moles of DDQ only **16** was isolated. It is noteworthy that in no case was the desired ketoacid **11b** produced. The tetraene **15** was readily transformed into **16** by further treatment with DDQ. An attempt to open the lactone ring in **16** by alkaline hydrolysis caused a retroaldol ring opening with formation of the diketoacid **19a**, in complete analogy with previous experience of Newman and Manhart[12] with a related compound. It is of incidental interest that the 5-*de*-methyl analog of **19a** had been reported by Sir Robert Robinson over 35 years ago.[13] Introduction of two double bonds solely into ring B was not facilitated by

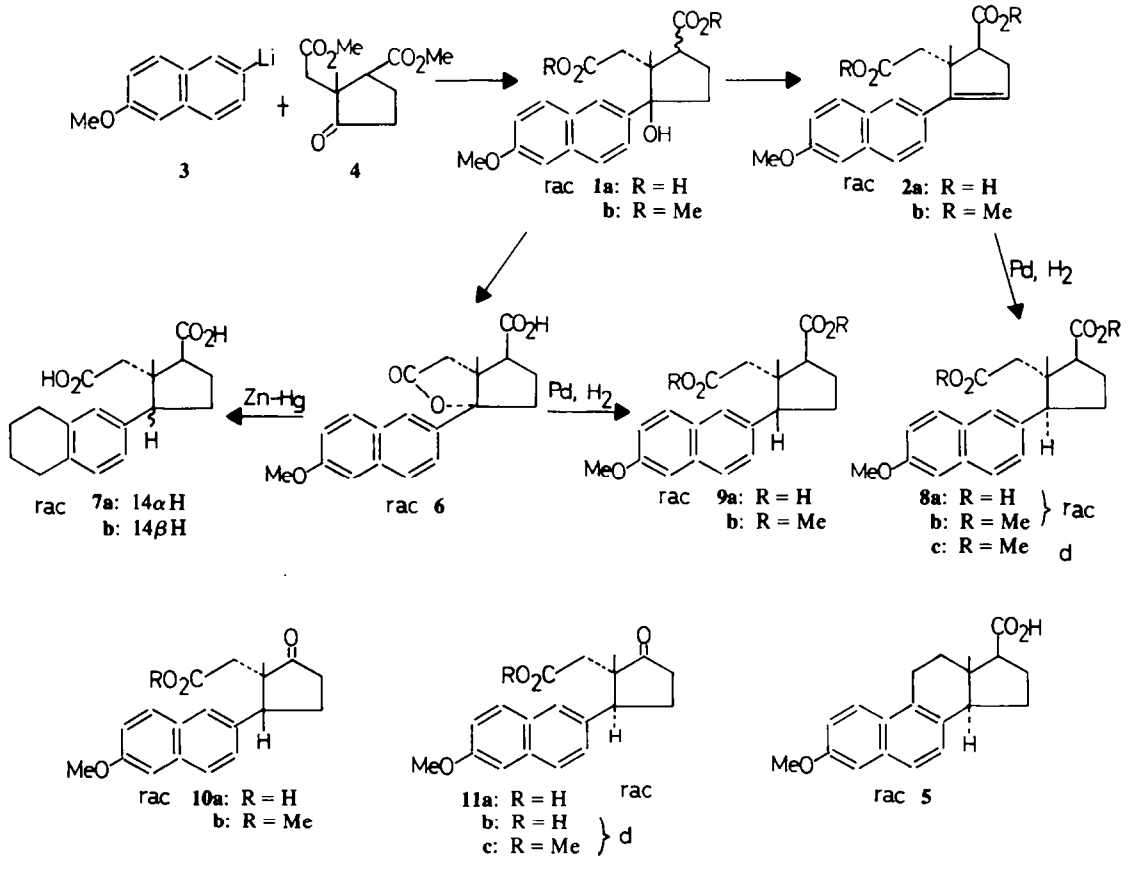


Chart 1.

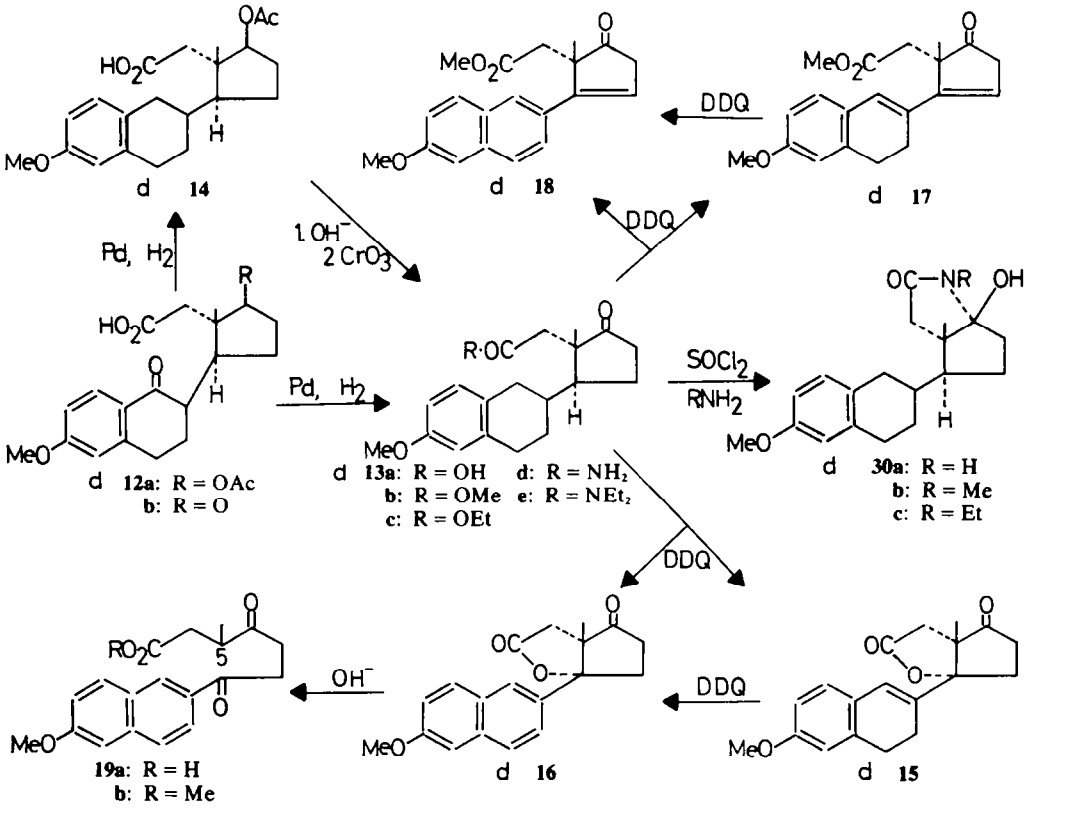


Chart 2.

employment of the methyl ester **13b**: with 2 moles of DDQ the pentaene **17** was obtained, while with 5 moles an impure sample of the hexaene **18** was isolated. The last product was also obtained by further treatment of **17** with DDQ. The above results indicate that dehydrogenation by DDQ of **13**, as acid or ester, proceeds in the order Δ^8, Δ^{14} and finally Δ^6.

We next set out to convert the acid **11b** into the dicarboxylic ester **8c**. To this end we first proceeded in the more accessible model series with ring B hydroaromatic. Attempts at conversion of the ketoester **13b** into the 17-aldehydo homolog by means of methoxymethyltriphenylphosphonium chloride and sodium methoxide or butyllithium[14] gave discouraging results. Equally unsuccessful was the treatment of the acid **13a**, the ester **13b** or the diethylamide **13e** with dimethylcarbamoyl lithium,[15] none of the expected 17-hydroxy-17-dimethylamido derivatives being obtained. Turning to the cyanohydrin approach (Chart 3), treatment of **13a** with potassium cyanide and acetic acid in ethanol afforded a mixture of the cyanolactone **20a** and the ethyl ester **13c**. Similar treatment of the methyl ester **13b** furnished the cyanolactone **20a** and the amidolactone **21a**, which must have formed by hydration of **20a**. In order to prevent lactonization of the cyanohydrin formed, attempts were made to prepare the cyanohydrin of the amide **13d**. This amide was prepared by the action of ammonia on the acid chloride of **13a**, but its IR spectrum, unlike that of the diethylamide **13e**, exhibited no 5-membered ring ketone absorption and pointed rather to the cyclic structure **30a**. Such formulation applies also to the corresponding monomethylamide **30b** and monoethylamide **30c**. When **30a**, originally thought to have the non-cyclic formula **13d**, was reacted in the standard manner with potassium cyanide and acetic acid in ethanol, the ethoxylactam **22a** was produced, again devoid of absorption of C_{17}-carbonyl expected at about 5·75 μ; when the reaction was run in methanol, the corresponding methoxylactam **22b** was obtained. This assignment of structures to compounds **30** and **22** finds support also in their mass-spectrometric behaviour discussed below, and in location of their C_{18}-Me signals: in the cyclic compounds **13a** and **e** they appear at 0·96 and 0·95 ppm, in the hydroxylactams **30a, b** and **c** at 1·12, 1·11 and 1·11 ppm, and in the alkoxylactams **22a** and **b** at 1·08 and 1·07 ppm, respectively. Finally, to circumvent this tendency to cyclization, the diethylamide **13b** was used to make the corresponding cyanohydrin, but only the starting material was recovered, even when liquid hydrogen cyanide and sulfuric acid were employed.

As expected, alkaline treatment of the cyanolactone **20a** caused reversal of the cyanohydrin reaction. On the other hand, heating **20a** or the amidolactone **21a** with methanol and sulfuric acid furnished the lactone ester **23a**. Attempts to remove the oxygen function from position 17 with zinc and acetic acid or with zinc amalgam were without avail, and so were efforts to eliminate it with phosphorus oxychloride in pyridine. Lactone ring opening with ammonia or diethylamine failed. Alkaline hydrolysis at temperatures up to 160° were fruitless, for acidification of the reaction mixture followed by esterification with diazomethane yielded only the starting lactone ester **23a**. Similarly, treatment of the alkaline hydrolysis mixture with methyl sulfate gave only the starting material. However, at 206° alkaline elimination of the hydroxyl group with formation of the Δ^{16} bond could be smoothly carried out, with concomitant cleavage of the 3-methoxy group. Esterification of the resulting diacid **25a** with diazomethane furnished the hydroxyester **26**. Similar conditions had been found by Wilds *et al.*[16] to be effective for elimination of the hydroxyl group in position 16 of the etioester **24**.

Turning back from the model to the naphthalenic series, the ester **11c** on treatment with potassium cyanide and acetic acid afforded a mixture of the cyanolactone **20b** and the amidolactone **21b**, which were separated and each converted with methanol-sulfuric acid into the lactone ester **23b**. Heating with potassium hydroxide in ethylene glycol at 206° gave smoothly the 16-dehydroacid **25b** which was treated with methyl sulfate and then with diazomethane to furnish the olefinic diester **27**. The UV spectrum showed the presence of the unconjugated methoxynaphthalene moiety, which excludes migration of the double bond to the 14,15-position.[16] The relationship of the angular Me group and the hydrogen at carbon 14 in **27** remained trans (Me signal at 0·89 ppm). Catalytic hydrogenation furnished the d-dimethyl ester **8c**, whose IR and NMR spectra were different from those of the racemic 14β ester **9b** obtained by hydrogenolysis of the lactone **6**. On the other hand, the mass spectra of **8c** and **9b** were identical except for the relative intensity of the peaks (Table 2).

In the 14β series, conversion of the racemic ketoester **10b** into the cyanolactone **28** proceeded smoothly, as well as the subsequent methanolysis to the ester **29**. However, in distinction from the 14α series, treatment of **29** with potassium hydroxide at 206°, followed by methylation with methyl sulfate and then diazomethane, gave a 10% yield of the Δ^{14} ester **2b**; none of the expected Δ^{16} ester could be obtained. At temperatures below 206° only the starting material could be recovered. It appears that in the 14β series any Δ^{16} ester produced is unstable at the temperature of formation and the double bond isomerizes to the conjugated 14,15 position, with extensive decomposition taking place. Retreatment of filtrates at 240° with potassium hydroxide in diethylene glycol gave only small amounts of isolable **2b**, in distinction from the behaviour of **24**.

In the course of this work certain regularities relating to the positioning of the C_{18}-Me signal were observed: (a) substitution of the nitrile by the carbomethoxy group (**28**→**29**; **20b**→**23b**; **20a**→**23a**) has an upfield effect of 0·35 to 0·4 ppm; (b) reversal of configuration at C_{14} from α to β (**7a**→**7b**; **8**→**9**; **20b**→**28**; **23b**→**29**) caused the expected[5] downfield change of 0·42–0·51 ppm.

Mass spectrometry. In previous reports it was shown[7,17] that the most intensive fragmentation of the 8(14)-seco steroids is due to the cleavage of the benzylic 9,11 bond. In sharp contrast to this behaviour the 9(11)-seco compounds containing the hydroaromatic ring B (**13a-c, 21a, 23a, 26**) undergo fracture of ring B by a retro-Diels-Alder reaction under electron bombardment, yielding ion **a** (Chart 4). The same fragmentation is also characteristic of tetraline[18] and its 2-alkyl derivatives.[19] Another feature is the successive elimination of ROH and CH_2CO from the molecular ions of **13a-c** and **26**, the last step being accompanied by the loss of two H atoms (Table 1). Interestingly, the compound **17** eliminates ROH and CH_2CO without hydrogen transfer, yielding an ion of *m/e* 252. In **13a-c, 26** and **17** the fragmentation sequences were substantiated by appropriate metastable transitions.

The major difference between the mass spectra of lactones **21a** and **23a** and spectra of their acid and ester analogs (**13a-c, 26**) is the lack of peaks due to ions M–ROH, M–ROH–CO and M–ROH–(CH_2CO + 2H). On

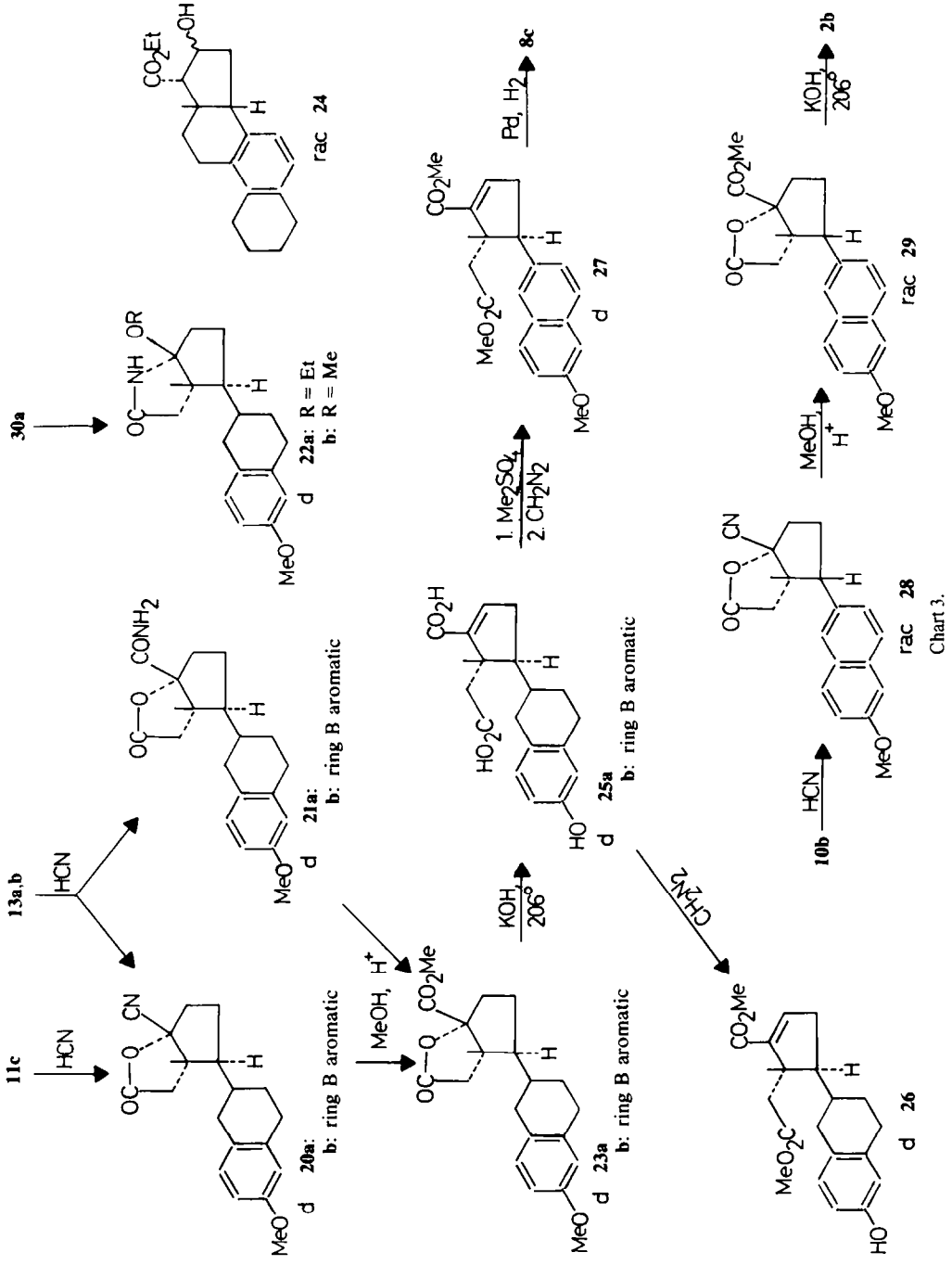
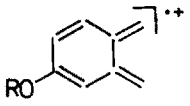
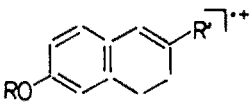

11c
HCN
13a,b
HCN
30a
MeOH, H+
KOH, 206°
1. Me2SO4
2. CH2N2
Pd, H2
8c
CH2N2
10b
HCN
MeOH, H+
KOH, 206°
2b
d 20a: b: ring B aromatic
d 21a: b: ring B aromatic
d 22a: R = Et b: R = Me
rac 24
d 23a b: ring B aromatic
d 25a b: ring B aromatic
d 27
d 26
rac 28
rac 29

Chart 3.



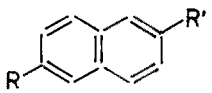
R = Me, *m/e* 134
R = H, *m/e* 120

a



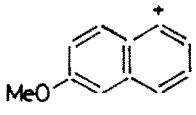
b: R = Me, R′ = H, *m/e* 160
R = H, R′ = H, *m/e* 146

c: R = Me, R′ = CH=CH$_2$, *m/e* 186
R = H, R′ = CH=CH$_2$, *m/e* 172



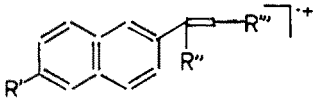
d: R = OMe, R′ = CH$_2$, *m/e* 171
R = H, R′ = CH$_2$,
1,2,3,4-tetrahydro (th), *m/e* 145

f: R = OMe, R′ = C≡O, *m/e* 185



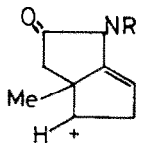
m/e 157

e



g: R′ = OMe, R″ = R‴ = H, *m/e* 184
R′ = OMe, R″ = OH, R‴ = H, *m/e* 200
R′ = R″ = R‴ = H, 1,2,3,4-th, *m/e* 158

h: R′ = OMe, R″ = H, R‴ = CH$_2$·, *m/e* 197
R′ = OMe, R″ = OH, R‴ = CH$_2$·, *m/e* 213
R′ = OMe, R″ = H, R‴ = CH$_2$⁻, 6,7,8,9-th, *m/e* 201
R′ = R″ = H, R‴ = CH$_2$·, 1,2,3,4-th, *m/e* 171



R = H, *m/e* 136
R = Me, *m/e* 150
R = Et, *m/e* 164

i

Chart 4.

Table 1. Relative intensities of the characteristic peaks in the mass spectra of seco steroids with hydroaromatic ring B

Compound	*m/e* (rel. intensity)						
	M·	M—ROH	M—ROH—CO	M—ROH—(CH$_2$CO + 2H)	*a*	*b*	*c*
13a	316	298[a]	270[a]	254[a]	134	160	186
	(100)	(15)	(6)	(34)	(77)	(61)	(25)
13b	330	298	270	254	134	160	186
	(100)	(26)	(7)	(40)	(20)	(57)	(19)
13c	344	298[b]	270[b]	254[b]	134	160	186
	(96)	(56)	(20)	(64)	(67)	(100)	(40)
21a	343	—	—	—	134	160	186
	(100)				(49)	(19)	(5)
23a	358	—	—	—	134	160	186
	(100)				(83)	(20)	(7)
26	358	326	298	282	120	146	172
	(40)	(40)	(28)	(70)	(25)	(100)	(10)
17	326	294	266	252[c]	—	—	—
	(100)	(15)	(32)	(54)	—	—	—

R = Me unless otherwise stated.
[a] R = H. [b] R = Et. [c] M—MeOH—CH$_2$CO.

the other hand both **13a-c**, **26** and **21a**, **23a** yield the abundant ions **b** and **c**, the well-known fragments of the mass spectra of estrone derivatives.[20] In contrast, ions **a-c** are absent from the spectrum of the 8,14-bisdehydro derivative **17**: clearly the two double bonds suppress both the retro-Diels-Alder reaction in ring B and the fracture of ring C.

The main feature of mass spectra of seco compounds containing aromatic ring B (Table 2) is the formation of ions **g** and **h**, originating from the breakdown of ring D. The Δ^{14} and Δ^{16} esters **2b** and **27** do not exhibit such type of fragmentation, the most abundant peaks being due to the loss of the C_{17}-side chain in the form of CH_3COOMe. This reaction also occurs in **9a**, **b** and **8c**, but to a lesser extent. In acids **7a** and **9a**, and in esters **9b**, **8c**, **2b** and **27** elimination of ROH, HCOOR and AcOR + HCOOR from the corresponding molecular ions is diagnostically important, there being no loss of these fragments in the corresponding lactones **6**, **16**, **23b** and **28**.

The 13,14-lactones (**6** and **16**) and the 14-hydroxyester **1b** reveal an intense formation of ions **e** and especially **f**, the latter stemming mainly from ion **g** (*m/e* 200). On the other hand, in 13,17-lactones **23b** and **28**, as well as in acids **9a**, **7a** and in esters **9b**, **8c**, formation of ions **e** and **f** is not observed. Finally, the shift of the mass number of ion **g** by 16 mass units (to *m/e* 200) on passing from **23b**

Table 2. Relative intensities of the characteristic peaks in the mass spectra of seco steroids with aromatic ring B

Compound	m/e (rel. intensity)									
	M^+	M—ROH	M—HCOOR	M—AcOR	M—AcOR—HCOOR	*d*	*e*	*f*	*g*	*h*
1b	386	354[a]	326	—	—	—	157	185	200	213
	(83)	(10)	(5)				(12)	(57)	(46)	(100)
6	340	—	—	—	—	—	157	185	200	213
	(100)						(25)	(69)	(48)	(17)
16	310	—	—	—	—	—	157	185	200	—
	(86)						(28)	(88)	(100)	
9a	342	324[b]	296[b]	282[b]	237[b]	171	—	—	184	197
	(100)	(7)	(6)	(34)	(18)	(34)			(23)	(82)
9b	370	338	310	296	237	171	—	—	184	197
	(100)	(7)	(9)	(51)	(38)	(24)			(24)	(48)
8c	370	338	310	296	237	171	—	—	184	197
	(100)	(10)	(12)	(64)	(34)	(24)			(32)	(48)
23b	354	—	—	—	—	171	—	—	184	197
	(100)					(18)			(28)	(89)
28	321	—	—	—	—	171	—	—	184	197
	(100)					(9)			(34)	(57)
7a	316	298[b]	270[b]	256[b]	211[b]	145	—	—	158	171
	(34)	(24)	(16)	(100)	(60)	(28)			(18)	(60)
2b	368	336	308	294	235	171	—	—	—	—
	(50)	(12)	(62)	(100)	(66)	(9)				
27	368	336	308	294	235	171	—	—	—	—
	(29)	(2)	(7)	(100)	(18)	(16)				

R = Me unless otherwise stated.
[a] *m/e* 369 (9%), M—H_2O; [b] R = H.

and **28** (or from **9a, b** and **8c**) to **6** and **16** (or to **1b**, Table 2), as well as high resolution exact mass measurements demonstrate the presence of an O atom in ion **g**, indicating that the lactone oxygens in **6** and **16** are joined to C_{13}.

While the ions **a-c** discussed above, characteristic of seco compounds with ring B hydroaromatic, are also present in the spectra of lactams **22a, b, 30a-c** (Table 3), the most intensive fragmentation of the latter involves formation of ion **I** (Chart 4) by loss of ethanol, methanol or water, respectively, from their molecular ions, followed by the cleavage of the 8,14 bond. However, the diethylamide **13e**, unlike **30a-c**, does not yield ion **i**; the most abundant peak in its spectrum is due to $CH_3CONEt_2^+$ (*m/e* 115, Table 3), providing additional evidence that **30a-c** exist as 17-hydroxylactams. Moreover, the corresponding shifts of the mass numbers of ions **i** in the spectra of **30b** and **c** as compared with those of **30a, 22a, b**, as well as high resolution mass spectrometry data are in accordance with the lactam structure proposed for these compounds. The differences between the structures of **30b, c** and their alkoxy isomers **22a,b** are reflected also in their corresponding spectra: while **30b** and **c** readily eliminate water on electron bombardment, **22a** and **b** lose methanol and ethanol respectively, no ejection of water being observed.

EXPERIMENTAL

M.ps are uncorrected. Optical rotations were measured in dioxane. NMR spectra were recorded on a Varian Associates A-60 instrument in $CDCl_3$, except where stated otherwise, using TMS as internal standard. Mass spectra were determined at 70 eV and 120–150° on an Atlas CH4 Mass Spectrometer equipped with a TO-4 ion source, using a direct inlet system. High resolution mass spectra were recorded on a Varian MAT 731 Mass Spectrometer

Table 3. Relative intensities of the characteristic peaks of amide **13e** and lactams **22a,b, 30a,b** and **30c**

Compound	m/e (rel. intensity)							
	M^+	M—H_2O	M—ROH	*a*	*b*	*c*	*h*	*i*
13e	371[a]	—	—	134	160	186	—	—
	(19)			(7)	(10)	(20)		
30a	315	297	—	134	160	186	201	136
	(100)	(48)		(70)	(84)	(68)	(10)	(74)
30b	329	311	—	134	160	186	—	150
	(15)	(99)		(10)	(6)	(7)		(100)
30c	343	325	—	134	160	186	201	164
	(15)	(41)		(24)	(19)	(28)	(10)	(100)
22a	343	—	297[b]	134	160	186	201	136
	(59)		(65)	(59)	(66)	(59)	(38)	(100)
22b	329	—	297[c]	134	160	186	201	136
	(100)		(80)	(60)	(88)	(73)	(30)	(100)

[a] Base peak: *m/e* 115, $(CH_3CONEt_2)^+$; [b] R=Et; [c] R=Me.

in conjunction with Spectro-System 100-MS, at the resolving power of 10,000 and 70 eV. Elemental compositions of all ions of the mass spectra discussed above were determined. Measurements of the metastable transitions in the first field free region were made with the MAT 731 spectrometer using the defocusing technique. Assay of samples was done with aid of IR, UV and NMR spectra, as well as the consistent use of TLC (Merck A.G. silica gel F-254 plates, with benzene-ethyl acetate mixtures ranging from 9:1 to 1:1; visualization of spots in UV light, iodine vapor and phosphomolybdic acid followed by sulfuric acid). The "dry" method was employed in column chromatography.

rac - 3 - *Methoxy* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11,17β - *dioic acid* (**8a**). A soln of **2b** (500 mg) in 90 ml EtOAc was hydrogenated with 400 mg of 5% Pd-C and 200 mg of precipitated $CaCO_3$ for 3 hr at room temp and 40 psi. The resulting product could not be crystallized even after column chromatography and was heated with a soln of 3·7 g KOH in 30 ml ethylene glycol for 3 hr at 140°. Water (200 ml) was added, the soln acidified with HCl and the resulting solid isolated with EtOAc (420 mg). It was twice recrystallized from acetone-benzene to furnish 250 mg of the still crude **8a**, m.p. 200–225°; λ_{max}^{KBr} 5·85 μ; NMR δ 0·72 (s, 3, 18-CH_3), 3·91 (s, 3, 3-OCH_3) and 7·52 (m, 6, arom). Further attempts at purification of the acid through the methyl ester were unsuccessful.

rac - 3 - *Methoxy* - 14β - *hydroxy* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11,17 - *dioic acid* (**1a**). The crude acidic fraction obtained as described[1] by saponification, followed by acidification of the filtrate, deposited from ether **1a** (4·5 g) m.p. 175–183°. The pure sample had m.p. 188–9° (ether); *m/e* 358; λ_{max}^{KBr} 5·75–5·90 μ; UV-unconjugated methoxynaphthalene moiety; NMR (CD_3OD) δ 1·30 (s, 3, 18-CH_3), 3·94 (s, 3, 3-OCH_3) and 7·56 (m, 6, arom). (Found: C, 67·18; H, 6·28. Calc. for $C_{20}H_{22}O_6$: C, 67·02; H, 6·19%.)

Esterification with diazomethane gave the previously reported[1] **1b**, m.p. 122–4°; NMR δ 1·22 (s, 3, 18-CH_3), 3·62 (s, 3, 13-$CH_2CO_2CH_3$), 3·78 (s, 3, 17-CO_2CH_3) and 3·97 (s, 3, 3-OCH_3).

rac - 3 - *Methoxy* - 14α - *hydroxy* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11,17β - *dioic acid lactone* (11→14) (**6**). Addition of 15 g of *p*-toluenesulfonic acid to a hot suspension of **1a** (6·95 g) in 1·4 l benzene caused immediate dissolution. After refluxing for 15 min the cooled mixture was washed with water and then concentrated. In two crops there was obtained a total of 5·43 g of **6**, m.p. 170–8°, which has a tendency to separate from benzene in several interconvertible crystalline forms melting from 173–3·5° to 177–180°. *m/e* 340. λ_{max}^{KBr} 5·65–5·90 μ, all having identical mobilities and NMR spectra, and affording the same methyl ester; UV-like **8c**. (Found: C, 70·69; H, 6·06. Calc. for $C_{20}H_{20}O_5$: C, 70·57; H, 5·92%.)

rac - 3 - *Methoxy* - 9(11) - *seco* - 14 - *isoestra* - 1,3,5(10),6,8 - *pentaen* - 11,17β - *dioic acid* (**9a**). A soln of **6** (813 mg) in 80 ml AcOH was hydrogenated in the presence of 0·8 ml $HClO_4$ (70%) and 2 g 5% Pd-C for 1 hr at 44 psi. The filtered soln was treated with 300 ml water and the mixture extracted with 3 × 60 ml portions benzene. The extract was washed well with water, concentrated to 10 ml and stored at room temp. Over a period of two weeks 4 crops of **9a** were collected, totalling 580 mg and melting in the 170–185° region. Of these the last two crops were slightly contaminated with **6**. The pure sample had m.p. 188–190° (benzene-acetone); *m/e* 342; λ_{max}^{KBr} 5·83–5·92 μ. (Found: C, 69·87; H, 6·60. Calc. for $C_{20}H_{22}O_5$: C, 70·16; H, 6·48%.)

The dimethyl ester **9b** (diazomethane) had m.p. 93–4° (pet. ether or MeOH); *m/e* 370; λ_{max}^{KBr} 5·80 μ; UV-like **8c**; NMR δ 1·20 (s, 3, 18-CH_3), 3·51 (s, 3, 13-$CH_2CO_2CH_3$), 3·71 (s, 3, 17-CO_2CH_3), 3·93 (s, 3, 3-OCH_3) and 7·47 (m, 6, arom). (Found: C, 71·10; H, 7·00. Calc. for $C_{22}H_{26}O_5$: C, 71·33; H, 7·08%.)

rac - 9(11) - *Secoestra* - 5(10),6,8 - *trien* - 11,17β - *dioic acid* (**7a**). A mixture of **6** (3 g), 750 ml toluene, 500 ml conc. HCl, 250 ml water and 100 g Zn amalgam was refluxed with mechanical stirring for 9 hr. Subsequently, every 9 hr over the following 27 hr, the mixture was treated with the same amounts of fresh Zn amalgam, HCl and water. The organic phase was diluted with an equal volume of EtOAc, washed with water and evaporated to an oil which deposited from ether-pet ether a total of 1·9 g of the crude acid, m.p. 173–182°. Further recrystallizations from the same mixture of solvents and then from EtOAc furnished 0·9 g, m.p. 188–190°; *m/e* 316; λ_{max}^{KBr} 5·80–5·90 μ; λ_{max}^{EtOH} 262, 268 and 277 nm (ϵ 1710, 740 and 1550); NMR δ 0·86 (s, 3, 18-CH_3) and 1·28 (s, indicating a content of above 5% of **7b**, 18-CH_3). (Found: C, 71·82; H, 7·49. Calc. for $C_{19}H_{24}O_4$: C, 72·12; H, 7·65%.)

d - 3 - *Methoxy* - 9,17 - *dioxo* - 9(11) - *secoestra* - 1,3,5(10) - *trien* - 11 - *oic acid* (**12b**) was prepared from **12a** rather than by direct oxidation of estradiol 3-methyl ether-17-acetate.[11a] A soln of crude **12a** (35 g) in 500 ml 5% KOH aq was heated on the steam-bath for 40 min, then cooled and acidified with conc HCl. The mixture was extracted with 3 × 200 ml portions of methylene chloride which was then washed with water, NaCl aq. and evaporated. The oil was dissolved in 500 ml acetone, and at 5° treated with 70 ml of the Jones reagent. After 8 min 7 ml of MeOH was added, followed, after further 3 min, by 2·5 l of water. The mixture was worked up with EtOAc and the residual gum crystallized from 120 ml ether to afford 14–15 g of **12b**, m.p. 153–5°. Recrystallization from EtOAc did not raise the m.p. (reported[11a] 158–160° from MeOH aq.); *m/e* 330; λ_{max}^{EtOH} 222 and 274 nm (ϵ 11,100 and 15,500) (reported[11a] 227 and 277nm (ϵ 11,700 and 15,500)).

d - 3 - *Methoxy* - 17 - *oxo* - 9(11) - *secoestra* - 1,3,5(10) - *trien* - 11 - *oic acid* (**13a**). A soln of **12b** (43 g) in 1050 ml AcOH containing 4 ml $HClO_4$ (70%) was hydrogenated at room temp and atm pressure for 2·5 hr in the presence of 10 g of 5% Pd-C. The filtered soln was concentrated *in vacuo* at 45° (bath temp) until a volume of 300 ml, and at 70° treated with 150 ml boiling water. The product was washed with 50% AcOH and finally with water to furnish 35·7 g of **13a**, 95% pure (TLC), m.p. 116–120°. The pure sample had m.p. 134–5° (ether); *m/e* 316; λ_{max}^{KBr} 5·72 and 5·87 μ; λ_{max}^{EtOH} 278 and 287 nm (ϵ 2300 and 2150); $[\alpha]_D^{25}$ +91° (*c* 0·905); NMR δ 0·96) (s, 3, 18-CH_3), 3·75 (s, 3, 3-OCH_3), 6·95 (m, 3, arom), and 8·20 (s, 1, COOH). (Found: C, 71·98; H, 7·49. Calc. for $C_{19}H_{24}O_4$: C, 72·12; H, 7·65%).

The methyl ester **13b** (diazomethane) had m.p. 104–6° (MeOH); *m/e* 330; λ_{max}^{KBr} 5·70–5·75 μ; $[\alpha]_D^{25}$ +93° (*c* 0·85). (Found: C, 72·79; H, 7·83. Calc. for $C_{20}H_{26}O_4$: C, 72·70; H, 7·93%.)

In an analogous manner **12a** was hydrogenolyzed to the *desoxyacid* **14**, m.p. 120–2° (ether); λ_{max}^{KBr} 5·80 and 5·91 μ; λ_{max}^{EtOH} 278 and 286 nm (ϵ 3000 and 2600). *Hydrolysis of* **14** and *Jones oxidation* were carried uneventfully as described above for the conversion of **12a** into **12b**, to give the ketoacid **13a**.

d - 3 - *Methoxy* - 14α - *hydroxy* - 17 - *oxo* - 9(11) - *secoestra* - 1,3,5(10),8 - *tetraen* - 11 - *oic acid lactone* (**11→14**) (**15**) and *d* - 3 - *methoxy* - 14α - *hydroxy* - 17 - *oxo* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11 - *oic acid lactone* (**11→14**) (**16**). A soln of **13a** (2 g; 64 mmole) in 500 ml benzene was refluxed for 30 min with 2·93 g (129 mmole) of DDQ. The hydroquinone was removed by filtration, the filtrate was washed with water, $NaHCO_3$ aq, water and evaporated. Chromatography on 110 g of silica gel, using benzene-EtOAc (6:1) gave first **16**, which on recrystallization from MeOH had m.p. 152–4°, 520 mg; *m/e* 310; λ_{max}^{KBr} 5·63 and 5·73 μ; λ_{max}^{EtOH} 231, 262, 270, 314 and 329 nm (ϵ 87,200, 5650, 5970, 1590 and 1940); $[\alpha]_D^{25}$ +151° (*c* 1·01); NMR δ 0·92 (s, 3, 18-CH_3), 2·75 (s, 2, CO-CH_2CH_2), 3·93 (s, 3, 3-OCH_3), and 7·53 (m, 6, arom). (Found: C, 73·38; H, 5·75. Calc. for $C_{19}H_{18}O_4$: C, 73·53; H, 5·85%.)

The lactone **16** was immediately followed by **15**, which was recrystallized from MeOH, m.p. 163·5–165°, 380 mg; λ_{max}^{KBr} 5·63 and 5·73 μ; *m/e* 312; λ_{max}^{EtOH} 278 nm (ϵ 17,600); NMR δ 1·13 (s, 3, 18-CH_3), 3·78 (s, 3, 3-OCH_3), 6·57 (broad s, 1, 9C), and 6·95 (m, 3, arom). (Found: C, 72·76; H, 6·39. Calc. for $C_{19}H_{20}O_4$: C, 73·06; H, 6·45%). The tetraene **15** exhibited a characteristic brown coloration with phosphomolybdic acid followed by a H_2SO_4 spray and heating at 110°.

Refluxing 148 mg of **15** in 25 ml of benzene with 389 mg (3·5 equivs) of DDQ for 1 hr afforded **16** which on crystallization from MeOH gave 82 mg of a pure sample.

1 - (6 - *Methoxy* - 2 - *naphthyl*) - 1,4 - *dioxo* - 5 - *methylhexan* - 6 - *oic acid* (**19a**). A soln of **16** (160 mg) in 15 ml 5% KOH in MeOH was refluxed for 20 min. Most of the solvent was removed *in vacuo*, 30 ml water was added, and the cooled soln was acidified with HCl. The collected solid was recrystallized from benzene or MeOH to furnish 107 mg, m.p. 126·5–130°. The analytical sample had m.p. 129–130·5°; *m/e* 328; λ_{max}^{KBr} 5·84–5·98 μ; λ_{max}^{EtOH} 238, 242,

255 and 308 nm (ε 37,700, 34,800, 29,600 and 13,500); NMR δ 1·26 (d, J = 7 Hz, CH_3–CH<), 3·92 (s, 3, 3-OCH_3) and 7·63 (m, 6, arom). (Found: C, 69·40; H, 6·00. Calc. for $C_{19}H_{20}O_5$: C, 69·50; H, 6·14%.)

The methyl ester **19b** (diazomethane) had m.p. 78–80° (MeOH); *m/e* 342; λ_{max}^{KBr} 5·75, 5·83, 5·94 and 6·10 μ; $[\alpha]_D^{25}$ +5·7° (*c* 0·78); NMR δ 1·27 (d, J = 7 Hz, CH_3–CH<), 3·67 (s, 3, $-CO_2CH_3$), 3·95 (s, 3, 3-OCH_3) and 7·60 (m, 6, arom). (Found: C, 69·89; H, 6·39. Calc. for $C_{20}H_{22}O_5$: C, 70·16; H, 6·48%.)

d - 3 - Methoxy - 17 - oxo - 9(11) - secoestra - 1,3,5(10),8,14 - pentaen - 11 - oic acid methyl ester (17) and *d - 3 - methoxy - 17 - oxo - 9(11) - secoestra - 1,3,5(10),6,8,14 - hexaen - 11 - oic acid methyl ester* (**18**). A soln of **13b** (1 g; 30·3 mmole) and DDQ (1·37 g; 60·4 mmol) in 160 ml benzene was refluxed for 1 hr. After workup and chromatography as described, the early solid fractions were combined and recrystallized from MeOH (charcoal) to afford a total of 450 mg of **17**, m.p. 129–134°. The pure sample had m.p. 134–5·5°; *m/e* 326; λ_{max}^{KBr} 5·74 μ; λ_{max}^{EtOH} 230, 232 and 312 nm (ε 14,900, 15,500 and 29,750); $[\alpha]_D^{25}$ −32·3° (*c* 0·94); NMR δ 1·37 (s, 3, 18-CH_3), 3·07 (s, 2, 16-CH_2), 3·53 (s, 3, 13-$CH_2CO_2CH_3$), 3·81 (s, 3, 3-OCH_3), 6·26 (t, J = 3·5 Hz, 1, 15C), 6·55 (broad s, 1, 9C) and 6·89 (m, 3, arom). (Found: C, 73·71; H, 6·84. Calc. for $C_{20}H_{22}O_4$: C, 73·60; H, 6·79%.)

When **13b** was treated with 5 equivs of DDQ under conditions described above, or when **17** was treated with 2 equivs of DDQ, the hexaene **18** could be obtained in low yield by chromatography, as above. The product, *m/e* 324, still contained some accompanying material of *m/e* 326 and could not be obtained pure. It had m.p. 118–123° (MeOH); λ_{max}^{KBr} 5·74 μ; λ_{max}^{EtOH} 235, 292 and 300 nm (ε 60,000, 6000 and 6000). (Found: C, 73·78; H, 6·33. Calc. for $C_{20}H_{20}O_4$: C, 74·05; H, 6·22%.)

Compounds **17** and **18** gave the same brown color reaction as **15**.

(A) *Transformations in the ring A aromatic series*

d - 3 - Methoxy - 17α - amino - 17β - hydroxy - 9(11) - secoestra - 1,3,5(10) - trien - 11 - oic acid lactam (**11 → 17**) (**30a**). A soln of **13a** (5 g) in 20 ml thionyl chloride was refluxed for 15 min, whereupon the deep-green soln was taken to dryness *in vacuo*. The residual dark gum was dried by several additions and evaporations of benzene, then dissolved in 45 ml of dry THF and treated with 250 ml liquid ammonia. Next day the mixture was worked up with water and methylene chloride, followed by chromatography on silica gel (benzene-acetone (1:1)) to afford **30a** (2·5 g) of m.p. 152–4° (methylene chloride) or 162–8° (EtOAc), both forms having identical IR spectra; *m/e* 315; λ_{max}^{KBr} 2·90–3·30, 5·85–6·05 and 6·22 μ; $[\alpha]_D^{25}$ +34° (*c* 0·68); NMR δ 1·12 (s, 3, 18-CH_3), 3·77 (s, 3, 3-OCH_3)and 6·97 (m, 3, arom). (Found: C, 72·09; H, 7·82; N, 4·33. Calc. for $C_{19}H_{25}NO_3$: C, 72·35; H, 7·99; N, 4·44%.)

d - 3 - Methoxy - 17 - oxo - 9(11) - secoestra - 1,3,5(10) - trien - 11 - oic acid diethylamide (**13e**) was obtained as above from the acyl chloride and diethylamine. The resulting oil was chromatographed (benzene-EtOAc, 1:1) to afford the product melting at 120–1° (heptane); *m/e* 371; λ_{max}^{KBr} 5·76, 6·08 and 6·19 (w) μ; $[\alpha]_D^{25}$ +39° (*c* 0·855); NMR δ 0·95 (s, 3, 18-CH_3), 1·02 (s, 3, NCH_2CH_3, J = 7 Hz), 1·25 (s, 3, NCH_2CH_3, J = 7 Hz), 3·28 (t, 2, NCH_2CH_3), J = 7 Hz), 3·32 (t, 2, NCH_2CH_3, J = 7 Hz), 3·73 (s, 3, 3-OCH_3) and 6·93 (m, 3, arom). (Found: C, 74·19; H, 8·99; N, 3·98. Calc. for $C_{23}H_{33}NO_3$: C, 74·36; H, 8·95; N, 3·77%.)

d - 3 - Methoxy - 17α - (N - methyl) - amino - 17β - hydroxy - 9(11) - secoestra - 1,3,5(10) - trien - 11 - oic acid lactam (**11 → 17**) (**30b**). The crude acid chloride, obtained as above from 720 mg of **13a**, was heated at 100° for 5 hr in 10 ml of pyridine with 10 g of methylamine hydrochloride. The following day the solvent was distilled *in vacuo* and the residue worked up with water and EtOAc. Chromatography on silica gel (benzene-acetone, 3:1), followed by recrystallizations from acetone gave **30b**, m.p. 160–185° (despite the wide m.p. this product, as well as the ethyl derivative **30c** described below, appeared as single spots in TLC); *m/e* 329; λ_{max}^{KBr} 3·07, 5·99, 6·22(w) and 6·33(w) μ; NMR δ 1·11 (s, 3, 18-CH_3), 2·78 (s, 3, 17-N-CH_3), 3·73 (s, 3, 3-OCH_3) and 6·80 (m, 3, arom). (Found: C, 73·09; H, 8·15; N, 4·46. Calc. for $C_{20}H_{27}NO_3$: C, 72·92; H, 8·26; N, 4·25%.)

The corresponding N-*ethyl lactam* **30c** was prepared in an analogous manner with ethylamine hydrochloride, m.p. 165–172° (acetone); *m/e* 343; λ_{max}^{KBr} 3·16, 6·07, 6·17 (w) and 6·32 (w) μ; NMR 1·11 (s, 3, 18-CH_3), 3·78 (s, 3, 3-OCH_3) and 6·87 (m, 3, arom). (Found: C, 73·71; H, 8·40; N, 4·00. Calc. for $C_{21}H_{29}NO_3$: C, 73·43; H, 8·51; N, 4·08%.)

d - 3 - Methoxy - 17α - hydroxy - 17β - cyano - 9(11) - secoestra - 1,3,5(10) - trien - 11 - oic acid lactone (**11 → 17**) (**20a**) and *d - 3 - methoxy - 17α - hydroxy - 9(11) - secoestra - 1,3,5(10) - trien - 11,17β - dioic acid lactone* (**11 → 17**) - 17 - *amide* (**21a**). A mixture of **13b** (1 g) 30 ml EtOH, 3 g KCN and 8 ml AcOH was refluxed for 3 hr, whereupon 2 g KCN was added and reflux continued for 5 hr. The following morning the mixture was poured into 100 ml water and the precipitated oil allowed to solidify. The product was chromatographed on silica gel (benzene-EtOAc, 9:1): first the cyanolactone **20a** was obtained which on crystallization from MeOH had m.p. 174–5°, 210 mg; *m/e* 325; λ_{max}^{KBr} 5·55 μ; $[\alpha]_D^{25}$ +74° (*c* 0·96); NMR δ 1·42 (s, 3, 18-CH_3), 3·73 (s, 3, 3-OCH_3) and 6·84 m, 3, arom). (Found: C, 73·60; H, 6·89; N, 4·20. Calc. for $C_{20}H_{23}NO_3$: C, 73·82; H, 7·12; N, 4·30%.)

Cyanolactone **20a** was followed by unchanged **13b**, 226 mg, m.p. 102-4° (MeOH). Further elution furnished the amide **21a**, which after recrystallization from EtOAc had m.p. 255–6°, 85 mg; *m/e* 343; λ_{max}^{KBr} 3·00–3·15, 5·60 (sh), 5·66, 5·85 (w) and 6·19 μ; $[\alpha]_D^{25}$ +26° (*c* 0·35); NMR (DMSO) δ 1·05 (s, 3, 18-CH_3), 3·71 (s, 3, 3-OCH_3), 6·78 (m, 3, arom) and 7·45 (broad s, 2, 17-$CONH_2$). (Found: C, 69·91; H, 7·10; N, 3·88. Calc. for $C_{20}H_{25}NO_4$: C, 69·95; H, 7·33; N, 4·08%.)

When the acid **13a** was employed instead of the ester **13b** in the cyanohydrin reaction, a 1:1 mixture of the cyanolactone **20a** with the *ethyl ester* **13c** was obtained, which was chromatographed as above. The ester **13c** had m.p. 79–80° (MeOH); *m/e* 344; λ_{max}^{KBr} 5·74 and 5·81 μ. (Found: C, 73·52; H, 8·32. Calc. for $C_{21}H_{28}O_4$: C, 73·22; H, 8·19%.)

d - 3 - Methoxy - 17α - amino - 17β - ethoxy - 9(11) - secoestra - 1,3,5(10) - trien - 11 - oic acid lactam (**11 → 17**) (**22a**). A soln of **30a** (500 mg) 1·5 g KCN, and 4 ml AcOH in 25 ml EtOH was refluxed for 16 hr, whereupon additional 3 g KCN and 8 ml of AcOH were added, and reflux was continued for 6 hr. The bulk of solvents was removed *in vacuo* and the residue was worked up with water and EtOAc, followed by chromatography of the solid on silica gel, using benzene-acetone (1:1). First the lactam **22a** was eluted, which on recrystallization from acetone had m.p. 170–4°, 285 mg. Further recrystallizations gave a wide-melting solid (184–191°), uniform in TLC; *m/e* 343; λ_{max}^{KBr} 3·24–3·35, 5·87, 6·05(w) and 6·22(w) μ; λ_{max}^{EtOH} 279 and 287 nm (ε 2100 and 1900); $[\alpha]_D^{20}$ +35·3° (*c* 1·0); NMR δ 1·08 (s, 3, 18-CH_3), 1·19 (t, J = 7 Hz, 17-OCH_2CH_3), 3·36 (q, J = 7 Hz, 17-OCH_2CH_3), 3·77 (s, 3, 3-OCH_3), 6·95 (m, 3, arom) and 7·91 (s, 1, 17-NHCO). (Found: C, 73·51; H, 8·40; N, 3·88. Calc. for $C_{21}H_{29}NO_3$: C, 73·43; H, 8·51; N, 4·08%.) Further elution afforded 63 mg of the starting amide **30a**, m.p. 147–9°.

The *17β-methoxy lactam* **22b** was obtained as above when EtOH was substituted by MeOH: 300 mg, m.p. 185–190° (acetone); *m/e* 329; λ_{max}^{KBr} 3·23–3·33, 5·87, 6·04 (w) and 6·20 (w) μ; λ_{max}^{EtOH} 278 and 289 nm (ε 2420 and 2270); $[\alpha]_D^{25}$ +27·3° (*c* 1·0); NMR δ 1·07 (s, 3, 18-CH_3), 3·23 (s, 3, 17-OCH_3), 3·75 (s, 3, 3-OCH_3), 6·80 (m, 3, arom) and 7·88 (s, 1, 17-NHCO). (Found: C, 72·65; H, 8·50; N, 3·96. Calc. $C_{20}H_{27}NO_3$: C, 72·92; H, 8·26; N, 4·25%.)

d - 3 - Methoxy - 17α - hydroxy - 9(11) - secoestra - 1,3,5(10) - trien - 11,17β - dioic acid lactone (**11 → 17**) - 17 - *methyl ester* (**23a**). A mixture of **20a** (190 mg) with 15 ml of a 2:1 soln (v/v) of MeOH in conc H_2SO_4 was heated on the stream bath for 5 hr. After 2 hr all solid was in soln. The following day the mixture was treated with ice-water and the solid (150 mg, m.p. 135–140°) was best purified by chromatography on silica gel (benzene-EtOAc, 9:1) to furnish **23a**, which after 2 recrystallizations from ether had m.p. 153–4°, 56 mg; *m/e* 358; λ_{max}^{KBr} 5·56 and 5·76 μ; $[\alpha]_D^{25}$ +48° (*c* 0·36); NMR δ 1·02 (s, 3, 18-CH_3), 3·71 (s, 3, 17-CO_2CH_3), 3·74 (s, 3, 3-OCH_3) and 6·75 (m, 3, arom). (Found: C, 70·29; H, 7·26. Calc. for $C_{21}H_{26}O_5$: C, 70·37; H, 7·31%.)

d - 3 - Hydroxy - 9(11) - secoestra - 1,3,5(10), 16 - tetraen - 11,17-dioic acid dimethyl ester (**26**). An extensive study of the effects of reaction time and temp on the progress of dehydration of **23a** by a 15% soln of KOH in ethylene glycol was carried out. The following procedure, represents the optimal conditions found,

shorter reaction times or lower temps giving varying amounts of the starting material. A soln of **23a** (320 mg) in 20 ml ethylene glycol containing 3 g KOH was refluxed for 6 hr at 206°. Water was added, the soln acidified with HCl and extracted with EtOAc. The crude 3-hydroxy-Δ^{16}-dicarboxylic acid was cautiously esterified with diazomethane at 0° (to minimize pyrazoline formation) and chromatographed on silica gel (benzene-EtOAc, 9:1 to yield 120 mg of **26**, m.p. 118–9°; *m/e* 358; λ_{max}^{KBr} 2·98 and 5·88 μ; $[\alpha]_D^{25}$ +42° (*c* 1·0); NMR δ 1·20 (s, 3, 18-CH_3), 3·51 (s, 3, 13-$CH_2CO_2CH_3$), 3·68 (s, 3, 17-CO_2CH_3) and 6·69 (m, 3, arom). (Found: C, 70·55; H, 7·15. Calc. for $C_{21}H_{26}O_5$: C, 70·37; H, 7·31%.)

(B) *Transformations in the rings A/B aromatic series*

d - 3 - *Methoxy* - 17 - *oxo* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11 - *oic acid methyl ester* (**11c**) was prepared from the acid **11b** with diazomethane, m.p. 115–8° (pet. ether); λ_{max}^{KBr} 5·73 and 5·79 μ. (Found: C, 73·36; H, 6·72. Calc. for $C_{20}H_{22}O_4$: C, 73·60; H, 6·79%.)

d - 3 - *Methoxy* - 17α - *hydroxy* - 17β - *cyano* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11 - *oic acid lactone* (**11 → 17**) (**20b**) and *d* - 3 - *methoxy* - 17α - *hydroxy* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11,17β - *dioic acid* - 17 - *amide* (**21b**). A soln of **11c** (14·5 g) and 43 g KCN in 430 ml EtOH containing 116 ml AcOH was refluxed for 8 hr. Over a period of 6 days fresh 43 g KCN, 430 ml EtOH and 116 ml AcOH were added each day and the mixture was refluxed for 8 hr. The product was poured into 5 l ice-water, taken up in ether and washed with water and $NaHCO_3$ aq. Chromatography on silica gel (770 g) afforded, with benzene-EtOAc 9:1, 4 g of **20b**. The pure sample (MeOH) had m.p. 154–5°; *m/e* 321; λ_{max}^{KBr} 5·59 μ; $[\alpha]_D^{25}$ +21° (*c* 1·5); NMR δ 1·13 (s, 3, 18-CH_3), 3·92 (s, 3, 3-OCH_3) and 7·48 (m, 6, arom). (Found: C, 74·93; H, 5·78; N, 4·59. Calc. for $C_{20}H_{19}NO_3$: C, 74·74; H, 5·96; N, 4·36%.)

The cyanolactone **20b** was followed by **11c**, (5·2 g). Occasionally partial overlapping of **20b** and **11c** necessitated fractional crystallization or rechromatography.

Elution with acetone yielded next the amide **21b**, which after recrystallization from EtOAc had m.p. 215–6°, 0·48 g; λ_{max}^{KBr} 5·61 (sh), 5·71 and 5·91 μ; $[\alpha]_D^{25}$ +100° (*c* 0·86); NMR δ 0·90 (s, 3, 18-CH_3), 3·90 (s, 3, 3-OCH_3) and 7·45 (m, 6, arom). (Found: C, 70·63; H, 6·18; N, 3·89. Calc. for $C_{20}H_{21}NO_4$: C, 70·78; H, 6·24; N, 4·13%.)

Occasionally **21b** was immediately followed by the acid **11b**, 1·4 g.

d - 3 - *Methoxy* - 17α - *hydroxy* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11,17β - *dioic acid lactone* (**11 → 17**) - **17** - *methyl ester* (**23b**). A mixture of **20b** (1·97 g) and 100 ml of a 2:1 soln (v/v) of MeOH in conc H_2SO_4 was heated for 4 hr on the steam bath. The following morning it was poured on a mixture of 300 g ice and 200 ml methylene chloride. The aqueous phase was twice reextracted with methylene chloride, the combined organic extracts were washed with water and $NaHCO_3$ aq, concentrated almost to dryness, and treated with 50 ml ether. The lactone **23b** which crystallized out (1·74 g) had a double m.p. 75–7° and 114°, was 85% pure (TLC) and suitable for the following reaction. Further recrystallizations from methylene chloride-ether gave a sample of m.p. 119–120°; *m/e* 354; λ_{max}^{KBr} 5·60 and 5·75 μ; $[\alpha]_D^{24}$ +19·4° (*c*, 1·0); NMR δ0·77 (s, 3, 18-CH_3), 3·80 (s, 3, 17-CO_2CH_3), 3·88 (s, 3, 3-OCH_3) and 7·45 (m, 6, arom). (Found: C, 71·32; H, 6·44. Calc. for $C_{21}H_{22}O_5$: C, 71·17; H, 6·25%.)

In an analogous manner the amide **21b** furnished **23b**.

d - 3 - *Methoxy* - 9(11) - *secoestra* - 1,3,5(10),6,8,16 - *hexaen* - 11,17 - *dioic acid dimethyl ester* (**27**). A soln of **23b** (1·54 g) and 3·3 g KOH in 25 ml ethylene glycol was refluxed for 6 hr, the temp of the boiling soln being maintained at 205–6°; until this temp was reached volatile components were allowed to distil off. The cooled soln was diluted with 100 ml water, treated with 14 g KOH, and at 25–30°, over a 1·5 hr period, 30 ml methyl sulfate was added dropwise with vigorous mechanical stirring, care being taken to maintain the reaction alkaline by further addition of KOH pellets when necessary. The mixture was then stirred for 1 hr, heated on the steam bath for 30 min, cooled, acidified with conc HCl, and extracted 3x with EtOAc. A gelatinous impurity was removed by filtration, the organic phase was washed with water and at 0° esterified with ethereal diazomethane. After several min the soln was taken to dryness *in vacuo* and the residue chromatographed on 50 g of silica gel using 5% EtOAc in benzene. There was obtained 650 mg of the solid diester **27**, which after recrystallization from pet ether had m.p. 93–6°, 555 mg. Further recrystallization raised the m.p. to 96–7°; *m/e* 368; λ_{max}^{KBr} 5·79 and 5·86 μ. λ_{max}^{EtOH} 230, 261, 272, 317 and 331 nm (ϵ 85,000, 6300, 6170, 1600 and 2060); $[\alpha]_D^{25}$ +11·4° (*c* 0·82); NMR δ 0·89 (s, 3, 18-CH_3), 3·71 (s, 3, 13-$CH_2CO_2CH_3$), 3·78 (s, 3, 17-CO_2CH_3), 3·91 (s, 3, 3-OCH_3) and 7·26 (m, 6, arom). (Found: C, 71·50; H, 6·39. Calc. for $C_{22}H_{24}O_5$: C, 71·72; H, 6·57%.)

d - 3 - *Methoxy* - 9(11) - *secoestra* - 1,3,5(10),6,8 - *pentaen* - 11,17β - *dioic acid dimethyl ester* (**8c**). A mixture of **27** (430 mg), 475 mg 5% Pd-C, 300 mg precipitated $CaCO_3$, and 50 ml MeOH was hydrogenated at 40 psi and room temp for 20 hr. The product was chromatographed on 24 g of silica gel using benzene-EtOAc (19:1) and recrystallized from MeOH to give 138 mg of m.p. 79–80° and 133 mg of m.p. 72–5°; *m/e* 370; λ_{max}^{KBr} 5·80 μ; λ_{max}^{EtOH} 230, 261, 271, 316 and 331 nm (ϵ 80,000, 6050, 6150, 1600 and 2050); $[\alpha]_D^{25}$ +10·2° (*c* 1·2); NMR δ 0·73 (s, 3, 18-CH_3), 3·69 (s, 6, 13-$CH_2CO_2CH_3$ and 17-CO_2CH_3), 3·91 (s, 3, 3-OCH_3) and 7·46 (m, 6, arom). (Found: C, 71·53; H, 6·85. Calc. for $C_{22}H_{26}O_5$: C, 71·33; H, 7·08%.)

rac - 3 - *Methoxy* - 17α - *hydroxy* - 17β - *cyano* - 9(11) - *seco* - 14 - *isoestra* - 1,3,5(10),6,8 - *pentaen* - 11 - *oic acid lactone* (**11 → 17**) (**28**). The acid **10a**[5a] (9·9 g) was treated with diazomethane and the oily ester **10b** in 325 ml EtOH and 88 ml AcOH was refluxed with mechanical stirring for 7 hr with 32 g of KCN. Equal amounts of EtOH, AcOH and KCN were added, and reflux was maintained for 8 hr. The workup was analogous to that of **20b**, and after chromatography on silica gel (benzene-EtOAc, 9:1) and crystallization of the early fractions from MeOH there was obtained 7·93 g of **28**, m.p. 147–150°; *m/e* 321; λ_{max}^{KBr} 5·60 μ; NMR δ 1·63 (s, 3, 18-CH_3), 3·93 (s, 3, 3-OCH_3) and 7·50 (m, 6, arom). (Found: C, 75·00; H, 6·11; N, 4·70. Calc. for $C_{20}H_{19}NO_3$: C, 74·74; H, 5·96; N, 4·36%.)

rac - 3 - *Methoxy* - 17α - *hydroxy* - 9(11) - *seco* - 14 - *isoestra* - 1,3,5(10),6,8 - *pentaen* - 11,17β - *dioic acid lactone* (**11 → 17**) - 17 - *methyl ester* (**29**). A mixture of **28** (7·92 g and 450 ml of a 2:1 solution (v/v) of MeOH in conc H_2SO_4 was heated for 7 hr on the steam bath, and the following ,morning worked up as described for **23b**. The product crystallized from ether-pet ether (2:1) and afforded a total of 5·8 g, m.p. 173–6°. Chromatography of the filtrates over silica gel furnished additional 0·27 g, m.p. 180–2°. The analytical sample (MeOH) had the same m.p.; *m/e* 354; λ_{max}^{KBr} 5·64 and 5·74 μ; NMR δ 1·28 (s, 3, 18-CH_3), 3·87 (s, 3, 17-CO_2CH_3), 3·94 (s, 3, 3-OCH_3) and 7·50 (m, 6, arom). (Found: C, 71·02; H, 6·01. Calc. for $C_{21}H_{22}O_5$: C, 71·17; H, 6·25%.)

rac - 3 - *Methoxy* - 9(11) - *secoestra* - 1,3,5(10),6,8,14 *hexaen* - 11,17β - *dioic acid dimethyl ester* (**2b**). The lactone **29** (5·7 g) was treated with KOH in ethylene glycol at 206°, then with methyl sulfate and finally with diazomethane exactly as described for **23b**. TLC showed the presence of at least 50% of the starting material and about 30% of **2b**. Chromatography on silica gel (benzene-EtOAc, 19:1) furnished in the first fractions 505 mg of **2b**, m.p. 107-9° (MeOH), identical with an authentic sample;[1] NMR 1·29 (s, 3, 18-CH_3), 3·51 (s, 3, 13-$CH_2CO_2CH_3$), 3·78 (s, 3, 17-CO_2CH_3), 3·93 (s, 3, 3-OCH_3), 4·55 (t, J = 3 Hz, 1, 15C) and 7·44 (m, 6, arom).

Heating the filtrates with 15 g of KOH in 100 ml of diethylene glycol at 240° for 4 hr, followed by methyl sulfate and diazomethane treatments, yielded a complicated oily mixture, TLC of which indicated presence of 10–15% of **2b**.

Acknowledgements—The authors are deeply obliged to Dr. Brain of Beecham Research Laboratories for a generous supply of the ketoacid **10a** and a sample of **11a**; to Betty Poplinger and Yosi Ben-Ephraim for technical assistance; and to Prof. Y. Mazur for helpful discussions.

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