Tetrahedron. Vol. 24, pp. 5881 to 5891. Pergamon Press 1968. Printed in Great Britain

HETEROCYCLIC STEROIDS—XII[1]

SYNTHESIS OF N-METHYL- AND N-ETHYL-6-AZA-8(14)-DEHYDROESTRONE METHYL ETHER

W. N. SPECKAMP, J. A. VAN VELTHUYSEN,[2] U. K. PANDIT and H. O. HUISMAN

Laboratory for Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands

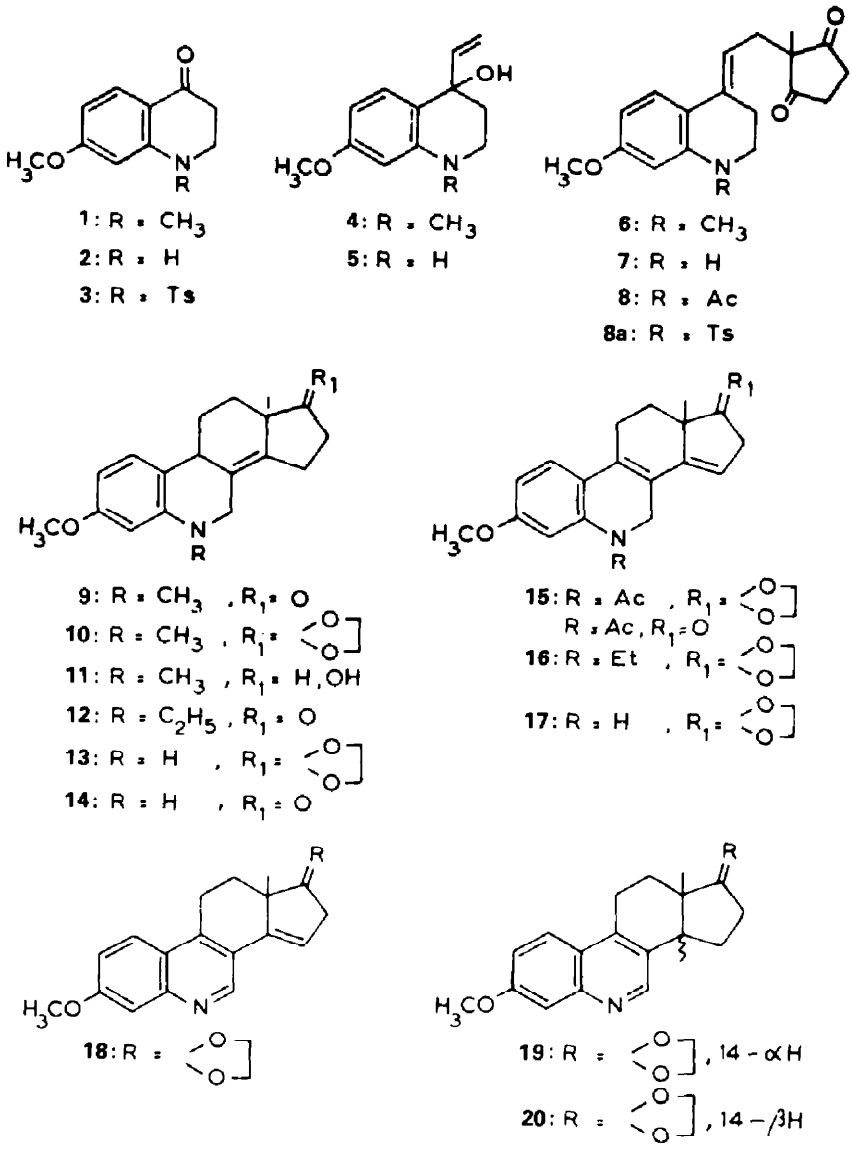
(*Received in the UK 5 April* 1968; *accepted for publication* 30 *April* 1968)

Abstract—The synthesis of N-methyl- and N-ethyl-6-aza-8(14)dehydroestrone is described and its structure proved spectroscopically. The mode of its formation is elucidated as being an acid-catalysed disproportionation of N-alkyl-6-aza-8(14)-bisdehydrosteroids. Several new 6-aza-steroids are described.

THE physiological importance of synthetic steroid analogues has led, in recent years, to the synthesis of a variety of modified steroid molecules, wherein one or more C atoms have been substituted by hetero atoms. A considerable share of this work is accounted for by the total synthesis of azasteroids, a subject, which continues to receive attention in this laboratory.[3] Our initial success in the development of a facile synthesis of the 6-aza-steroid skeleton[4] has prompted us to undertake the elaboration of the scheme to include, amongst others, the preparation of 6-aza-19-nor-androstane derivatives.[5] Preliminary results of this investigation have been presented in an earlier communication.[6] N-methyldihydroquinolone (**1**) was conveniently synthesized via a modification of a recently described reaction scheme,[7] namely, addition of propiolactone to N-methyl-*m*-anisidine, followed by PPA catalysed ring closure of the resulting N-methyl-N-(*p*-methoxyphenyl)-β-amino-propionic acid. Two other routes, both involving methylation of amino ketone **2** as the last step suffered from serious practical problems—preparation of amino ketone **2**, according to Atwal,[8] gave in our hands an inseparable mixture of *ortho* and *para* cyclization products and, the approach involving detosylation of ketone **3**[9] resulted in such low overall yields so as to make the procedure synthetically unattractive.

Addition of vinylmagnesium bromide to **1** gave alcohol **4** as a yellow unstable oil, which solidified at temperatures below −20°. At room temperature the product underwent rapid decomposition; consequently, a freshly prepared sample of **4** was allowed to react with 2-methylcyclopentanedione-1,3 in benzene and t-butanol, whereupon a quantitative yield of the moderately stable diketone **6** was obtained. A crystalline sample of **6** melted at 61–67° and showed the expected spectral characteristics. The high yield of the condensation products suggests a particularly facile reaction which is attributed to the availability of the nitrogen lone pair of electrons*. The presence of the basic N atom however, demands the ring closure of the seco-steroid **6** to be carried out in polar solvents, in order to prevent a precipitation of the

* For a discussion of some factors involved in this type of addition see Ref. 3 and J. C. Hubert, W. N. Speckamp and H. O. Huisman, *Tetrahedron Letters* a forthcoming paper.



salt. Furthermore, the reaction required the use of more than one equivalent of an acid. Of the various conditions which were attempted, three sets of conditions were found to be equally successful. Upon treatment of diketone **6** with 1·5 equivalents of *p*-toluenesulfonic acid in nitromethane and chromatography of the dark oily product over alumina, a crystalline material was obtained which had CO absorption at 1735 cm^{-1}. The UV spectrum showed no absorption higher than 294 nm and possessed characteristics similar to those of 7-methoxy-N-methyl-1,2,3,4-tetrahydroquinoline. A molecular-ion peak at *m/e* 297 in the mass spectrum of the product and the absence of vinylic protons in the NMR spectrum (Fig. 1) suggested the

8(14)-dehydro structure **9** for the compound, its formation being rationalized in terms of successive cyclization and disproportionation steps. This somewhat unexpected process was further studied by varying the nature of the solvent and acid catalyst in the cyclization reaction. Isolation of a 16% yield of **9** from cyclization of

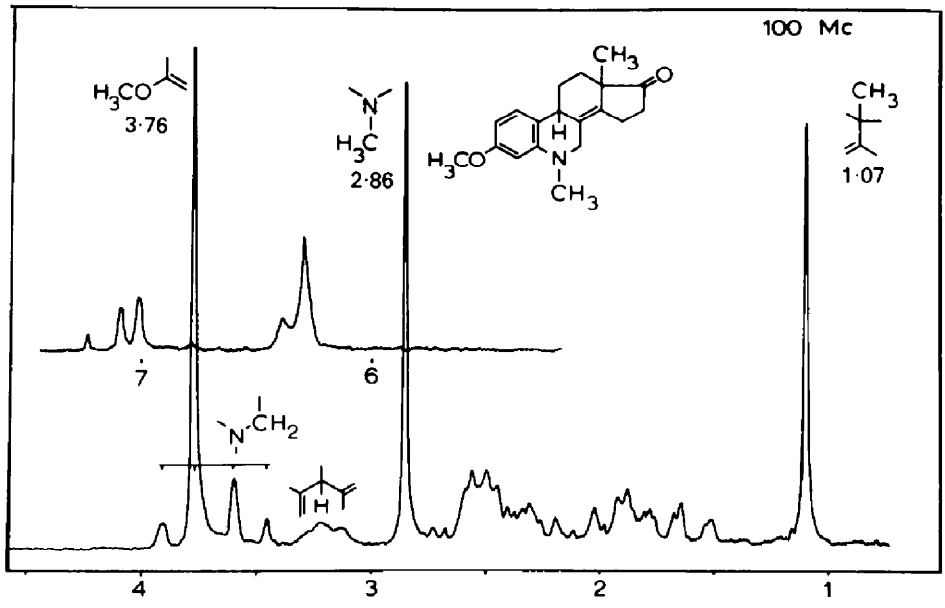


FIG. 1

6 in hydrochloric acid–tetrahydrofuran made it evident that nitromethane could not have seriously influenced the disproportionation step. When the cyclization reaction was carried out in ethylene glycol the ethylene ketal **10** was obtained in 16% yield. The latter was quantitatively converted into ketone **9** upon hydrolysis. A possible role of the C_{17} keto group thus also seemed to be unlikely. Sodium borohydride reduction of **9** afforded the alcohol **11** as a crystalline solid, which turned out to be a very unstable compound decomposing readily into a mixture of non-identifiable unsaturated products upon standing.*

Neither treatment with acid, nor catalytic hydrogenation under concomittant isomerization conditions effected any change in the structure of ketone **9**. Corroborating evidence for the structure of ketone **9** was sought in the NMR and mass spectra of a series of 6-aza-steroidal derivatives. According to well documented rules[11] the influence of the 8(14)-dehydro system on the chemical shift of the C_{18}-Me protons expresses itself in a paramagnetic shift of 0·175 ppm. Recently, a further substantiation of this rule was found in the spectra of several estrane derivatives.[12] The Me absorptions in 8(14)-dehydroestrone and in the corresponding C_{17} alcohol display chemical shift differences of 0·20 ppm when compared with their saturated analogues. As is shown in Table 1, the C_{18}–Me absorptions of the 8(14)-dehydro-6-aza-steroids are

* A corresponding behaviour has also been reported for 8(14)-dehydroestradiol methyl ether-3.[10]

in full accord with the expected values. Moreover, a close resemblance between carbocyclic and heterocyclic steroids may be noted.

TABLE 1

Compound	C_{18}	Expected*	Difference
9	1·07	1·07	0
10	1·07	1·07	0
11	0·89		
12	1·11	1·07	0·04
13	1·10	1·07	0·03
8(14)-Dehydroestrone methylether (3)[10]	1·10	1·07	0·03
8(14)-dehydro-estradiol methyl ether (3)[12]	0·90		

* Based on the deshielding parameter of 0·18 ppm for the 8(14)-dehydro system. Expected chemical shift values are calculated by adding the latter factor to the value for the corresponding saturated analogue.

Finally, an indirect proof of the location of the double bond was found in the mass spectra of ketones **9** and **12**. Both spectra display high M^+, $M-1^+$, $M-15^+$ and $M-29^+$ peaks, while prominent $M-28^+$ and $M-123^+$ ions are also present (Fig. 2). Most significant in terms of the anticipated retro Diels–Alder fragmentation[13] are the peaks at *m/e* 269 (M − 28) and *m/e* 268 (M − 29). In the spectrum of ketone

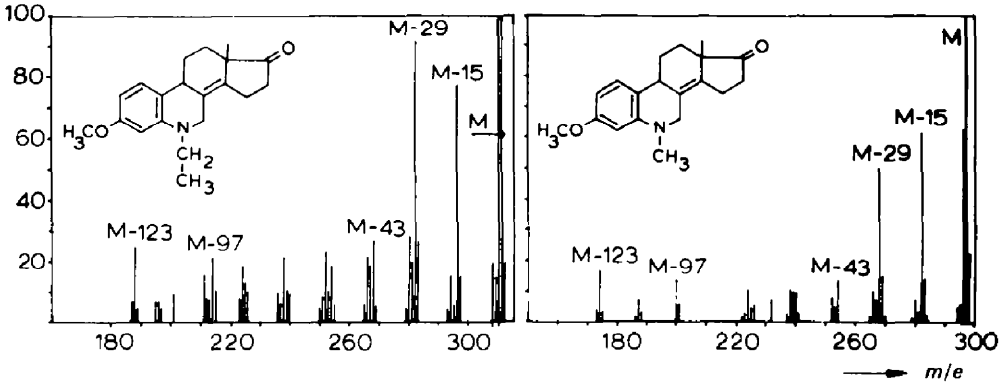
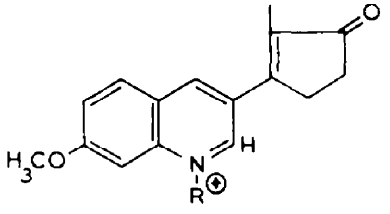


FIG. 2

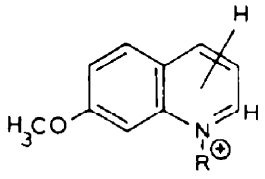
9 a metastable peak at 243·8 evidenced the occurrence of the process 297 → 269 + 28 (calc. 243·6). Exact mass determination revealed the composition of ion *m/e* 269 as $C_{17}H_{19}NO_2$(M—C_2H_4). Corresponding measurements for the *m/e* 268 fragment proved that it consisted of a mixture of $C_{18}H_{22}NO$(M—HCO)* and $C_{17}H_{18}NO_2$(M—C_2H_5) ions of which the latter probably represents the resonance-stabilized structure

* The high M—HCO peak reflects the known tendency of the loss of CO from C_{17}-steroidketones.[14] In ketones **9** and **12** the C_{13}–C_{17} cleavage is facilitated by the activating influence of the 8,14 double bond.

21. Also of interest in the spectra of ketones **9** and **12** is the high intensity of the $M - 123^+$ ion, which reflects the particular stability of the N-alkylquinolinium fragment **22**, the genesis of which may be visualized via a loss of the cyclopentenone moiety from ion *m/e* 269. The observation of a pronounced retro Diels–Alder fragmentation, which is absent in the decomposition patterns of estrone[15] and 6-aza-estrone,[5] fits in with the presence of the 8(14)-dehydro structure. The formation of



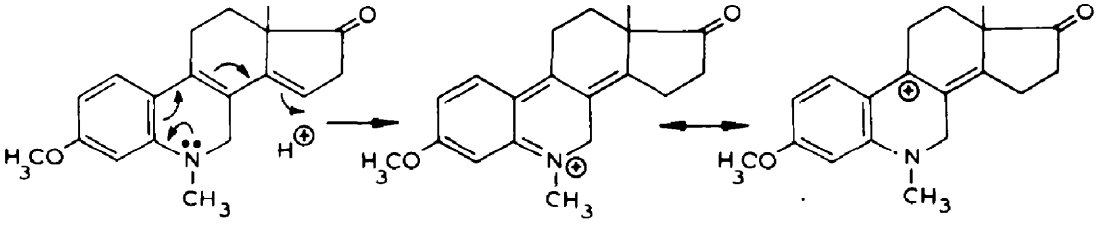
21:



22:

ketone **9** under conditions where both the 8(14)-seco intermediates, for the ring A aromatic steroids and N-tosyl-6-aza-steroids, give the corresponding 8(14)-bis-dehydro-steroidal compounds deserves some comment. The latter observation strongly suggests that the free electron pair on the nitrogen in **6** may play an important role in diverting the reaction path to a new product. An explanation for this consideration is outlined in Scheme 1.* Normal acid-catalyzed cyclization of **6** should yield the tetracyclic system **23**, which, in the carbocyclic series or the N-tosyl-6-aza series, is the end product of the reaction. However, when the nitrogen is present as a tertiary amine function, a further reaction of **23** with acid becomes possible. Such a reaction can either lead to protonation on the nitrogen or—via electronic relay of the nitrogen lone pair—at the end of the conjugated enamine system on C_{15}. The resulting ion is a resonance stabilized species which can be described in terms of structures **24a** and **24b**. Amongst the various courses of reaction open to **24b** is

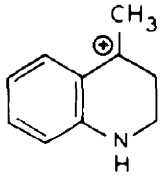
SCHEME 1



23: **24a**: **24b**:

* In a personal communication, Prof. A. I. Meyers, Louisiana State University, New Orleans, has suggested that formation of **9** via **23**, could involve an initial rearrangement of **23** to the 7,14-bisdehydro system, followed by protonation and disproportionation. While our results do not allow us to exclude such a mechanism we do not see (a) any particular advantage in invoking the latter sequence to explain the product and (b) the driving force necessary for the proposed rearrangement which takes a double bond out-of-conjugation from the aromatic ring.

that of disproportionation in which a hydride ion (presumably from C_7 of **23**) is transferred to the electropositive centre at C_9. A number of disproportionation reactions of analogous nature have been recently described in the literature,[16] a specially pertinent example being that of the quinoline system **25**. A possible way



25:

of testing this hypothesis is the synthesis of the diene system **23** and its subjection to acid treatment. Since it is well known that cyclization of N-tosyl dione **8a** proceeds normally and affords the corresponding 8,14-bisdehydro system[18] a route was chosen whereby an initially located electron-attracting substituent on the N atom of the seco-diketone could be easily converted into an alkyl group without the use of acidic conditions. The vinyl alcohol **5**, obtained via reaction of ketone **2** with an excess of vinyl magnesium bromide, was directly condensed with methylcyclopentanedione-1,3. Acylation of the seco-dione **7** with acetyl chloride and pyridine led to the oily N-acetyldione **8**, which was not purified. Initial cyclization experiments under conditions where the N-tosyl analogue **8a** could be easily cyclized, failed. Simultaneous ring closure and ketalization, coupled with prolonged reaction times finally afforded ketal **15** in 50% yield. The structure of **15** was proved by its NMR and mass spectra. In the latter, characteristic fragments at *m/e* 367 (molecular ion peak), *m/e* 324 (M-43, loss of acetyl), *m/e* 295 (M-72, loss of ethylene ketal) and *m/e* 252 (M-115, combined loss of both fragments) were prominent. A comparison with the mass spectrum of the 6-aza-equilenin ketal **19** showed a remarkable correspondence of the decomposition patterns, which in fact is to be expected after loss of the acetyl moiety from **15**. Furthermore, the presence of a vinylic proton in the NMR spectrum (δ 5·70 ppm) and a UV maximum at 315 nm (ε = 20,000) confirmed the presence of 8,14-bisdehydro system. Acid hydrolysis of ketal **15** afforded **15a** the spectral data of which also agreed with the 8,14-bisdehydro structure.

Upon treatment of **15** with potassium hydroxide a mixture of ketals **17** and **18** was obtained, from which after chromatographic separation **18** was isolated and converted into the known 6-aza-equilenin methyl ether via the following route: catalytic hydrogenation produced a mixture of 14α and 14β isomers, which were chromatographically separated and hydrolysed to the 6-aza-17-keto steroids.

Finally, the acetyl substituent in ketal **15** was converted into the Et group by reduction with LAH in ether. Careful chromatography over alumina afforded the N-ethyl ketal **16** as yellow-green prisms, m.p. 127–129° together with a little quantity of the ketal **18**. The structure of ketal **16** was evidenced by the following spectral data. The NMR spectrum exhibited a diffused triplet at δ 5·40 ppm showing the presence of an olefinic proton; the UV spectrum showed an absorption at 376 nm (ε 9900) and finally a molecular ion peak at *m/e* 353 was found in the mass spectrum. LAH

reduction of **15** in tetrahydrofuran resulted in a mixture of the following products—ketal **17** (12·3%) and ketal **18** (64·7%). The same behaviour is observed in the reduction of model dihydroquinolines.* Ketal **17**, which was also obtained by hydrolysis of the N-acetyl derivative **15**, underwent isomerization upon treatment with a palladium catalyst. The isolated products were ketal **18** (59·4%) and ketal **13** (8%). The latter product could have been only formed via a disproportionation of the 8,14-bisdehydro system, a reaction which is of the same type as observed before in the acid cyclization of the seco-dione **6**. Its structure was unequivocally proved by its direct synthesis via ring closure of the dione **7** in ethylene glycol.

Upon treatment of the ketal **16** with hydrochloric acid in ethanol a dark green oil was obtained from which ketone **12** could be isolated in a yield comparable to the one obtained in the direct acid cyclization of the analogous seco-dione **6**. Its spectral characteristics were identical to those of ketone **9**, thus proving the presence of the 8(14)-dehydro structure.

This result strongly supports the postulated reaction pathway. The stereochemistry of C_9 deserves some comment. While no definite evidence can be brought to bear upon the configuration of C_9-H, the suggested formation of **9** by a disproportionation mechanism implies the involvement of a second steroidal molecule as the hydride donor. Since such a hydride donor will be expected to approach from the less-hindered α-side of the intermediate **24b**, the preferred formation of the C_9-α-H isomer may be anticipated. The failure to detect a second isomer, despite deliberate chromatographic investigation of the reaction mixture, is in conformity with the tentative stereochemical assignment at C_9.

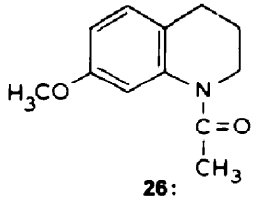
EXPERIMENTAL

All m.p.s are uncorrected. UV spectra in EtOH were determined on a Zeiss RPQ 20C spectrophotometer. IR spectra were measured in KBr pellets (unless otherwise stated) and were determined on a Perkin–Elmer Model 125 spectrophotometer. NMR spectra have been recorded on a Varian A-60 spectrometer using $CDCl_3$ as a solvent and TMS as a standard. Mass spectra were taken on a AEI Ms-9 double focussing mass spectrometer.

1-Methyl-1,2,3,4-tetrahydro-4-oxo-7-methoxyquinoline **1**

N-methyl-N-(*m*-methoxyphenyl)-2-amino-propionic acid (115 g)—prepared from 82 g of N-methyl-*m*-anisidine and 48 g of propiolactone, which were dissolved in 200 ml acetonitrile†, refluxed for 3 hr and vacuum distilled—and 1830 g of polyphosphoric acid were gently heated at 110° for 20 min. After pouring in ice water (5 l.) the solution was basified to pH = 9. After extraction with benzene an oil was obtained

* In the model system **26** two different solvents were used in the LAH reduction of the N-acetyl function. In ether exclusive conversion into an Et group took place,[19] while in THF the major process was the cleavage of the N-acetyl bond.



26:

† All organic solvents were purified and dried before use.

which on distillation gave 61 g of **1**, b.p. 130–160°/0·1 mm Hg. Recrystallization from benzene–pet ether afforded 50·4 g of yellow crystals m.p. 84–85°. (Found: C, 68·9; H, 7·0; N, 7·3; $C_{11}H_{13}O_2N$ requires: C, 69·05; H, 6·85; N, 7·33%); C=O absorption in IR spectrum at 1663 cm^{-1}; UV maxima were found at 211 (8000), 251·5 (24,000), 280·5 (10,600) and 368 (5700) nm.

2-[2[1]-(N-*Methyl*-7-*methoxy*-1,2,3,4-*tetrahydroquinolylidene*)-*ethyl*]-2-*methylcyclopentanedione*-1,3 **6**

Compound **4** (20·8 g) which was prepared from 17·8 g of **1** according to the described procedure[18] and 11·6 g of 2-methyl-cyclopentanedione-1,3 were refluxed for 1 hr in a mixture of 100 ml benzene, 60 ml t-BuOH and 4·6 ml triton B (40% in MeOH). After dilution with 200 ml ether, the organic soln was successively washed with 5% KOH aq, water and sat. NaCl aq yielding 29·1 g of **6** as a dark yellow syrup. Recrystallization from benzene–pet. ether afforded white crystals, m.p. 61–67°. (Found: C, 72·6; H, 7·4; N, 4·3; O, 15·5; $C_{19}H_{23}NO_3$ requires: C, 72·82; H, 7·39; N, 4·47; O, 15·32%). UV spectrum 235 (20,600), 253 (18,500), 273 (15,700) and 338 (5500) nm. The NMR spectrum showed singlets at δ 1·14 (C—Me), 2·83 (NMe) and 3·74 (OMe) and a triplet at 6·12 (=CH) ppm.

(±)-6-*Aza*-3-*methoxy*-6-*methylestra*-1,3,5(10),8(14)-*tetraene*-17-*one* **9**

Method A. 23·3 g of *p*-TsOH was added to a soln of 27·1 g of **6** in 480 ml nitromethane. After stirring for 2 hr at 80°, 1700 ml benzene and 300 ml sat. $NaHCO_3$ aq were added and the organic layer washed repeatedly with water and sat. NaCl aq. The oil obtained after evaporation of the solvent was chromatographed (cyclohexane-EtOAc 9:1) over 100 g of Al_2O_3. The second fraction gave upon crystallization from EtOH white crystals m.p. 144–145°. (Found: C, 76·8; H, 7·9; N, 4·6; O, 10·8; $C_{19}H_{23}NO_2$ requires: C, 76·73; H, 7·80; N, 4·71; O, 10·76%). The IR shows carbonyl absorption at 1735 cm^{-1}, and the UV the follwoing maxima: 216 (32,000), 251 (9700) and 294 (4700) nm.

Method B. A soln of 9·44 g of **6** in 135 ml THF and 30 ml HCl (1:1) was allowed to stand at room temp for 40 hr. After dilution with 100 ml ether and neutralization with sat. $NaHCO_3$ aq the waterlayer was extracted with benzene and the combined organic layers washed with water and sat. NaCl aq. Evaporation afforded an oil which was chromatographed over Al_2O_3 (cyclohexane–EtOH acetate 9:1) to yield 1·43 g of **9**.

(±)-6-*Aza*-3-*methoxy*-17,17-*ethylenedioxyestra*-1,3,5(10),8(14)-*tetraene* **10**

Compound **6** (29·1 g) and *p*-TsOH (24·4 g) in 500 ml toluene were refluxed for 5 min, after which a mixture of 4·5 g *p*-TsOH in 700 ml freshly distilled ethylene glycol was added. Upon additional refluxing for 5 hr, 500 ml benzene was added and the mixture treated with sat. $NaHCO_3$ aq. After extraction of the bicarbonate layer with benzene, the combined organic solns were evaporated and the residue chromatographed over 600 g Al_2O_3, (cyclohexane–EtOAc 19:1 and 3:1), which afforded 4·3 g of **10**, m.p. 144–146°, after crystallization from EtOH. (Found: C, 73·8; H, 8·2; N, 4·2; O, 14·0; $C_{21}H_{27}NO_3$ requires: C, 73·87; H, 7·97; N, 4·10; O, 14·06%); UV: 215 (34,000), 252 (7600) and 293 (5200) nm. NMR: δ 1·07 singlet (C—Me), 2·82 singlet (NMe), 3·73 singlet (OMe) and 3·88 singlet (OCH_2CH_2O) ppm.

From ketone **9**. 0·957 g of **9**, dissolved in a mixture of 1·02 g *p*-TsOH, 26 ml ethylene glycol and 20 ml toluene were refluxed for 5 hr. After cooling 50 ml benzene was added, and the soln extracted twice with sat. $NaHCO_3$ aq. After extraction of the water layer with benzene, and washing the combined organic solns with water and sat. NaCl aq, the benzene was evaporated and the residue crystallized from EtOH, yield 1·014 g, m.p. 144–146°.

6-*Aza*-3-*methoxy*-6-*methyl*-17β-*hydroxyestra*-1,3,5(10),8(14)-*tetraene* **11**

A mixture of 0·5 g $NaBH_4$, 1 g of **6**, 25 ml EtOH and 2 ml water was stirred overnight at room temp. After adding 25 ml water and neutralization with AcOH, the soln was extracted with ether. After washing the ether with water and sat. NaCl aq, the solvent was evaporated to afford 0·905 g of **11**, m.p. 98–105°, after crystallization from MeOH–water; IR: 3540 cm^{-1} (OH); UV: 216(28,000), 252 (8900) and 292 (4850) nm. NMR: δ singlets at 0·89 (C—Me) 2·82 (NMe) and 3·76 (OMe) ppm. Mass spectrum: molecular ion peak at *m/e* 299.

(±)-6-*Aza*-3-*methoxy*-6-*ethylestra*-1,3,5(10),8(14)-*tetraene*-17-*one* **12**

A soln of 1 g of **16** in 50 ml EtOH and 50 ml 0·3N HCl was refluxed for 0·5 hr. Upon cooling sat. $NaHCO_3$ aq was added till pH = 7 and the mixture extracted with $CHCl_3$. After washing the $CHCl_3$ phase with water and sat. NaCl aq, the solvent was evaporated and the dark green oily residue chromato-

graphed over 30 g Al_2O_3 (cyclohexane–EtOAc 19:1). The first fraction afforded 0·16 g of crystalline material, recrystallized from EtOH, m.p. 77–79°. (Found: C, 77·0; H, 8·1; N, 4·6; O, 10·4; $C_{20}H_{23}NO_2$ requires: C, 77·13; H, 8·09; N, 4·50; O, 10·28%); IR: 1734 cm^{-1} (C=O); UV: 218 (53,000), 254 (17,800) and 299 (7550) nm; NMR: δ 1·11 singlet (C_{18}—Me), 1·21 triplet (C—Me), 3·77 singlet (OMe) ppm.

(±)-6-*Aza*-3-*methoxy*-17,17-*ethylenedioxyestra*-1,3,5(10),8(14)-tetraene **13**

Compound **17** (1·61 g) and prehydrogenated Pd/$CaCO_3$ (2%; 3·5 g) in 40 ml THF, were shaken during 40 hr in an atmo of H_2. After removal of the catalyst and evaporation of the solvent, 1·57 of solid residue was obtained, which after chromatography over 100 g alumina (cyclohexane–EtOAc 10:1) afforded 0·13 g of **13** m.p. 180–182°, after recrystallization from cyclohexane. (Found: C, 73·2; H, 7·6; N, 4·4; O, 14·8; $C_{20}H_{25}NO_3$ requires: C, 73·36; H, 7·70; N, 4·28; O, 14·66%); IR: 3370 cm^{-1} (N—H); UV: 216 (39,000), 250 (6700) and 290 (1750) nm.

The product **13** was also obtained via cyclization of 36·5 g of **7** and subsequent chromatography of the reaction product, as described in the procedure for the cyclization of **6**, yield 0·02 g, m.p. 180–182°.

6-*Aza*-3-*methoxy*-6-*acetyl*-17,17-*ethylenedioxyestra*-1,3,5(10),8-14-*pentaene* **15**

Compound **2** (30 g) 350 ml THF was added to a suspension of vinylmagnesium bromide in 320 ml THF and 135 ml ether prepared from 22·5 g Mg and 129 g vinylbromide at −15°. After stirring overnight at room temp and additional heating at 50–55° during 2 hr, the soln was poured on a mixture of ice and NH_4Cl, the organic phase separated and the water layer extracted with $CHCl_3$.

The combined organic solns were washed with sat. NaCl aq, and dried upon $MgSO_4$. After evaporation of the solvent 35 g of oily **7** remained, which was used directly in the next step.

2-Methyl-cyclopentanedione-1,3 (22·5 g) was added to a soln of 35 g of **7** in 195 ml benzene and 110 ml t-BuOH. After stirring for 15 min at room temp, 8·6 ml Triton B-soln (40% in MeOH) was added and refluxed for 2 hr at 80°. Upon dilution with 200 ml benzene, 200 ml ether and 100 ml THF, the soln was extracted with 5% KOH aq, water and sat. NaCl aq. Drying over $MgSO_4$ and evaporation of the solvent yielded 36·5 g of a yellow syrup.

Acetylchloride (10·5 ml) was added slowly to a soln of 34·8 g of **7** in 105 ml pyridine and 70 ml benzene at 0°. After additional stirring for 15 min at room temp, 150 ml water was added and the mixture extracted with benzene. The benzene soln was repeatedly extracted with 10% HCl, 5% KOH aq, water and sat. NaCl aq, and finally dried over $MgSO_4$. Evaporation of the solvent gave 25·1 g of oily **8**; IR: ($CHCl_3$) 1760, 1720 and 1650 cm^{-1} (C=O).

A soln of 23·8 g of **8** and 3·6 g *p*-toluenesulfonic acid in 500 ml toluene was refluxed for 10 min under azeotropic water removal, after which 3·6 g *p*-toluenesulfonic acid in 500 ml ethylene glycol were added and the mixture refluxed for 5 hr. After cooling, 300 ml benzene was added and the soln extracted twice with sat. $NaHCO_3$ aq. After repeated extraction of the bicarbonate soln with benzene, the combined organic phase was washed with water and sat. NaCl aq and dried over $MgSO_4$. Evaporation of the solvent and chromatography of the oily residue over 750 g of alumina (cyclohexane–EtOAc 5:1) afforded 12·8 g of **15**. Crystallization from EtOH gave the pure compound, m.p. 151–153°. (Found: C, 71·8; H, 6·8; N, 3·9; O, 17·5; $C_{22}H_{25}NO_4$ requires: C, 71·91; H, 6·86; N, 3·81; O, 17·42%); IR: 1652 cm^{-1} (C=O); UV 220 (13,500); 256 (23,500); 261·5 (23,500) and 315 (20,000) nm. The NMR showed singlets at δ 1·05 (C_{18}-Me); 2·20 (CO—Me); 3·79 (OMe); a 4 proton singlet at 3·93 (OCH_2CH_2O), and a diffused triplet (=CH) at 5·70 ppm.

(±)6-*Aza*-3-*methoxy*-6-*acetylestra*-1,3,5(10),8-14-*pentaene*-17-*one* **15a**

Compound **15** (0·340 g) was dissolved in a mixture of EtOH HCl (1:1) and refluxed for 30 min. After cooling, sat. $NaHCO_3$ aq was added and the soln extracted with water, dried oven $MgSO_4$ and the solvent evaporated. Crystallization of the residue from EtOH afforded 0·186 g of needles, m.p. 130–133°. (Found: C, 74·3; H, 6·5; N, 4·4; O, 15·1; $C_{20}H_{21}NO_3$ requires: C, 74·28; H, 6·55; N 4·33; O, 14·84%); IR: 1737, 1657 cm^{-1} (C=O); UV: 257 (21,000), 262 (21,000) and 315 (17,000) nm. NMR: singlets at δ 1·13 (CMe), 2·28 (COMe) and 3·87 (OMe), diffused triplet at 6·08 (=CH) ppm.

(±)-6-*Aza*-3-*methoxy*-6-*ethyl*-17,17-*ethylenedioxyestra*-1,3,5(10),8-14-*pentaene* **16**

Compound **15** (9·63g) in 200 ml ether was added to a mixture of 2·5 g of LAH in 200 ml ether and the resulting soln refluxed for 2 hr. Upon cooling EtOAc and sat. Na_2SO_4 aq were added, the ppt filtered off and the filtrate evaporated. Chromatography of the resulting oil over 350 g alumina (cyclohexane–EtOAc 19:1,

resp. 4:1) gave a green oil, which after crystallization from EtOH afforded 4·5 g of green-yellow crystals m.p. 127–129°. (Found: C, 74·8; H, 7·7; N, 4·0; O, 13·8; $C_{22}H_{27}NO_3$ requires: C, 74·75; H, 7·70; N, 3·96; O, 13·58%). In the UV-spectrum absorptions were found at: 214 (20,000), 250 (24,500), 268 (33,000), 300 (8500) and 376 (9900) nm. NMR: singlets at δ 1·03 (C_{18}—Me) and 3·78 (OMe) a four proton singlet at 3·96 (OCH_2CH_2O), triplet at 1·16 (C—Me) and a diffused triplet at 5·40 (=CH).

(±)-6-*Aza*-3-*methoxy*-17,17-*ethylenedioxyestra*-1,3,5(10),8-14-*pentaene* **17**

A mixture of 2·3 g of **15**, 0·6 g KOH and 12 ml aqueous EtOH (90%) was refluxed for 16 hr. After adding water, the resulting ppt was filtered off and chromatographed over 110 g alumina, (cyclohexane–EtOAc 19:1, resp. 9:1 and 4:1). Crystallization of the first fraction from EtOH afforded 0·3 g of yellow crystals m.p. 142–147°. (Found: C, 73·8; H, 7·1; N, 4·4; O, 14·8; $C_{20}H_{23}NO_3$ requires: C, 73·82; H, 7·12; N, 4·30; O, 14·75%). UV: 254 (21.600), 309 (15,300) and 350 (5900). In the NMR spectrum singlets were found at δ 1·09 (C—Me) and 3·76 (OMe) one four proton singlet (O—CH_2CH_2—O) at 3·94, and a diffused triplet of one proton (=CH) at 5.41.

As a second product 1·28 g of **18** was isolated, m.p. 174–175°, after crystallization from EtOH.

6-*Aza*-3-*methoxy*-17,17-*ethylenedioxyestra*-1,3,5(10),6,8-14-*hexaene* **18**

Compound **15** (1·83 g) in 12 ml THF was added slowly to a solution of 0·48 g LAH in 12 ml THF and after stirring the mixture for 45 min, the excess LAH was decomposed by adding EtOAc and sat. NaCl aq. The ppt was filtered off, washed with THF, and the combined filtrates dried over $MgSO_4$. Evaporation of the solvent yielded an oil, which was chromatographed over 200 g alumina (cyclohexane–EtOAc 19:1, resp. 9:1). The first product eluted was **17**, m.p. 145–149°. The second fraction contained 1·043 g of **18**. Crystallization from EtOH afforded a pure compound, m.p. 174–175°. (Found: C, 74·1; H, 6·6; N, 4·4; O, 14·9; $C_{20}H_{21}NO_3$ requires: C, 74·28; H, 6·55; N, 4·33; O, 14·8%). In the UV spectrum the characteristic absorptions of the quinoline moiety appeared at 330 (3450), 345 (5400) and 360 (4650) nm. The NMR showed the following singlets: δ 1·08 (C_{18}—Me), 3·94 (OMe), 3·97 (OCH_2CH_2O) 9·11 (C_7—CH) ppm. A diffused triplet at δ 6·24 was assigned to the vinylic hydrogen.

(±)6-*Aza*-3-*methoxy*-14α-H-17,17-*ethylenedioxyestra*-1,3,5(10),6,8-*pentaene* **19**

Compound **18** (1·0 g) dissolved in 40 ml THF was hydrogenated over 1 g of Pd/C with uptake of 75 ml (calc. 76 ml) After filtration and evaporation of the solvent, the residue was chromatographed over 80 g alumina and successively eluted with mixtures of cyclohexane-EtOAc (19:1; 9:1). As a first fraction 0·25 g of the 14-β isomer was obtained. The second fraction consisted of a mixture of 14-α and 14-β isomers, while the third fraction afforded, after crystallization from cyclohexane the pure 14-α isomer, m.p. 144–145°. (Found: C, 73·7; H 7·1; N, 4·4; O, 14·8; $C_{20}H_{23}NO_3$ requires: C, 73·82; H, 7·12; N 4·30; O, 14·75%); UV: characteristic absorptions at 327 (4700) and 339 (5000) nm. NMR: δ 0·73 singlet ($C_{18}CH_3$); 3·92 singlet of 7 protons, (OMe + OCH_2CH_2O); 8·55 singlet (7-CH) ppm.

Acknowledgements—One of us (J. A. van Velthuysen) gratefully acknowledges financial support of the "Stichting voor Organisch Onderzoek" during his investigations. We wish to express our sincere appreciation to Drs. P. J. van der Haak, Drs. N. M. M. Nibbering, Drs. K. Spaargaren and Mr. C. Kruk of our Spectroscopy Department for helpful assistance with the NMR, Mass, UV and IR spectra. We are indebted to Messrs. H. Pieters and W. J. Buis of our Microanalytical Department for carrying out the microanalyses.

REFERENCES

[1] Heterocyclic steroids XI, R. van Hes, U.K. Pandit and H. O. Huisman, *Rec. Trav. Chim.* **86**, 1255 (1967).
[2] Part of the thesis of J. A. van Velthuysen, University of Amsterdam 1965.
[3] H. O. Huisman, *Bull. Soc. Chim. Fr.* 13 (1968).
[4] W. N. Speckamp, H. de Koning, U. K. Pandit and H. O. Huisman, *Tetrahedron* **21**, 2517 (1965).
[5] Heterocyclic Steroids XIII, W. N. Speckamp, J. A. van Velthuysen, M. A. Douw, U.K. Pandit and H. O. Huisman, *Tetrahedron* **24**, 5893 (1968).
[6] J. A. van Velthuijsen, M. A. Douw, W. N. Speckamp, U. K. Pandit and H. O. Huisman, *Tetrahedron Letters* 3081 (1966).
[7] J. Koo, *J. Org. Chem.* **28**, 1134 (1963).

[8] M. S. Atwal, L. Bauer, S. N. Dixit, J. E. Gearien and R. W. Morris, *J. Med. Chem.* **8**, 566 (1965).
[9] W. N. Speckamp, U. K. Pandit and H. O. Huisman, *Rec. Trav. Chim.* **82**, 39 (1963).
[10] W. F. Johns, *J. Org. Chem.* **31**, 3780 (1966).
[11] R. F. Zürcher, *Helv. Chim. Acta* **46**, 2054 (1963).
[12] L. Re, D. B. R. Johnston, D. Taub and T. B. Windholz, *Steroids* **8**, 365 (1966).
[13] H. Budzikiewicz, J. I. Brauman and C. Djerassi, *Tetrahedron* **21**, 1855 (1965).
[14] L. Tökes, R. T. LaLonde and C. Djerassi, *J. Org. Chem.* **32**, 1012 (1967).
[15] C. Djerassi, J. M. Wilson, H. Budzikiewicz and J. W. Chamberlin, *J. Am. Chem. Soc.* **84**, 4544 (1962).
[16] [a] J. Dreux and J. P. Quillet, *Bull. Soc. Chim. Fr.* 645 (1966);
[b] B. D. Tilak, R. B. Mitrao and C. V. Deshpande, *Tetrahedron Letters* 3569 (1965).
[17] B. D. Tilak, T. Ravindranathan and K. N. Subbaswami, *Ibid.* 1959 (1966).
[18] H. O. Huisman, W. N. Speckamp and U. K. Pandit, *Rec. Trav. Chim.* **82**, 898 (1963).
[19] V. M. Micovic and M. Mihailovic, *J. Org. Chem.* **18**, 1190 (1953).