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HETEROCYCLIC STEROIDS—IV[1]

TOTAL SYNTHESIS OF SOME 6-AZA-ESTROGENS

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Abstract—The syntheses of 6-aza-equilenin, 6-aza-estrone and the corresponding C-17 alcohols have been achieved from N-tosyl-6-aza-8, 14-bisdehydroestrone methyl ether (I). Also available via I are the 14β-isomers of the latter estrogens.

The partial synthesis of steroidal derivatives with altered or additional functional groups has led to the development of several clinically important compounds.[3] More recently, considerable interest has been directed to the modification of the steroid nucleus itself. Such modifications have frequently assumed the form of a replacement of a carbon atom of the cyclopentanoperhydrophenanthrene system by an atom of another element.[4] Other types of alterations have involved the extension of the steroid nucleus with additional rings[5] and expansion[6] or contraction[7] of one of the rings of the original system. A number of the compounds resulting from these types of modifications have proved to be of potential physiological interest.[8]

In this laboratory a programme on the total synthesis of heterocyclic steroids has been initiated which aims at the preparation of steroidal analogues containing one or more atoms of nitrogen, oxygen or sulphur in various nuclear positions. The physiological study of a series of such systematically modified steroids may be anticipated to provide an insight into the structure-activity relationship in this novel class of compounds. As the initial phase of this study we wish to report the total synthesis of several 6-aza-estrogens.

A convenient starting material for the synthesis of various 6-aza-19-nor-steroids described in the sequel is the N-tosyl ketone I which has been reported earlier.[9]

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[1] Part III. U. K. Pandit, W. N. Speckamp and H. O. Huisman, *Tetrahedron* in press; See also Part II, H. O. Huisman, W. N. Speckamp, H. de Koning and U. K. Pandit, *Tetrahedron Letters* 1275 (1964).

[2] Part of the thesis of W. N. Speckamp. University of Amsterdam, September (1964).

[3] [a] A. Bowers, L. Cuellar Ibanez and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 5991 (1959); [b] H. J. Ringold, J. Perez Ruelas, E. Batres and C. Djerassi, *Ibid.* **81**, 3712 (1959); [c] R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson and Clarissa Carabateas. *Ibid.* **83**, 1478 (1961).

[4] [a] R. Pappo and C. J. Jung, *Tetrahedron Letters* 365 (1962); [b] N. J. Doorenbos and C. L. Huang, *J. Org. Chem.* **26**, 4106 (1961); [c] R. B. Bloomfield and T. L. Jacobs, *J. Amer. Chem. Soc.* **82**, 4033 (1960); and Refs cited therein.

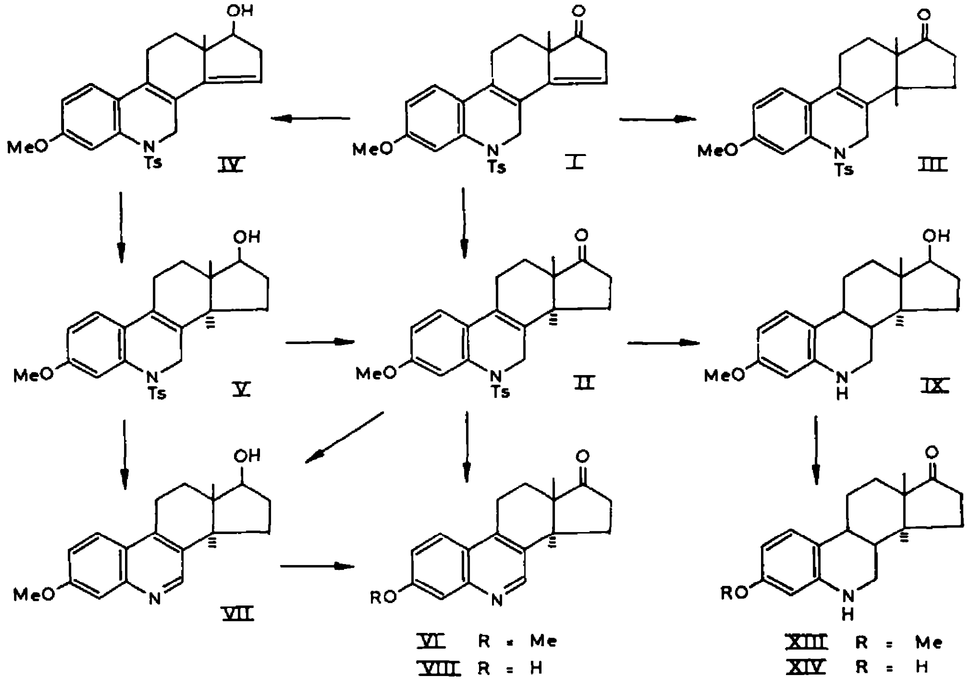
[5] [a] E. Caspi and D. M. Piatak, *Chem. & Ind.* 1984 (1962); [b] K. Brückner, K. Irnscher, F. V. Werder, K. H. Bork and H. Netz. *Chem. Ber.* **94**, 2897 (1961); [c] L. I. Smith, *J. Med. Chem.* **6**, 330 (1963).

[6] A. K. Bose, G. Mina, M. S. Manhas and E. Rzucidlo, *Tetrahedron Letters* 1467 (1963).

[7] [a] G. R. Pettit and P. Hofer, *Helv. Chim. Acta* **46**, 2142 (1963); [b] G. Muller and Chanh Huynh, French pat. 1,359,619; *Chem. Abstr.* **61**, 13382 c (1964); [c] O. Wintersteiner and M. Moore, *Tetrahedron* **20**, 1947 (1964).

[8] R. Hirschmann, N. G. Steirberg, J. H. Fried, R. Ellis, G. J. Kent and M. Tishler, *J. Amer. Chem. Soc.* **86**, 1520 (1964).

[9] H. O. Huisman, W. N. Speckamp and U. K. Pandit, *Rec. Trav. chim.* **82**, 898 (1963).



Catalytic reduction of I over Pd-$CaCO_3$ resulted in the formation of a mixture of two isomeric 14,15-dihydro-ketones which were separated by fractional crystallization. Stereochemical assignments of these isomers were made on the basis of their NMR spectra. The isomer exhibiting the C-18 methyl resonance at a δ value of 0·60 ppm is assigned the 14α- or C/D *trans* configuration (II) and the one showing its analogous angular methyl at a lower field (0·84 ppm) the 14β- or C/D *cis* configuration (III). This assignment derives its origin from the expected shielding of the C-18 methyl by the C_8-C_9 double bond in the 14α-isomer II. A similar argument has been utilized by Steele *et al.*[10] for stereochemical assignments in anthrasteroid series where the field associated with the aromatic ring B is considered to cause a diamagnetic shift of the C-18 methyl in the 14α-series.[11]

Contrary to the observation in the analogous carbocyclic system,[12] the ratio (NMR) of the isomeric ketones II and III obtained upon hydrogenation of I, indicates, that the predominant course of the catalytic reduction is one which results in the 14β-ketone III. Employment of other catalyst-carrier mixtures such as Pd-$SrCO_3$ or Pd-C did not significantly alter the isomeric ratio, while attempts to hydrogenate I over PtO_2 or over Ni_2 catalysts were unsuccessful, presumably owing to the poisoning of the metal by the sulphonamide moiety. In view of the striking difference between the stereochemical course of the reduction of tosyl ketone I and a corresponding normal steroidal skeleton, some comment on the influence of the tosyl substituent may be pertinent. Inspection of a molecular model of I suggests that while the C-18 methyl provides a

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[10] J. Steele, L. A. Cohen and E. Mosettig, *J. Amer. Chem. Soc.* **85**, 1134 (1963).

[11] N. S. Bhacca and D. H. Williams, *Applications of NMR spectroscopy in organic chemistry* Sect. 6-5; p. 151. Holden-Day, Amsterdam (1964).

[12] T. B. Windholz, J. H. Fried and A. A. Patchett, *J. Org. Chem.* **28**, 1092 (1963).

definite hinderance to the approach of the molecule from its β- side to the catalyst surface, the bulky tosyl group presents a considerable barrier to the alignment of the catalyst also to the α- side of the steroidal plane.[13] The tosyl group, consequently, inspite of its remoteness from the reaction site, is able to exert appreciable influence on the transformations in ring D. A further implication of such an influence is suggested from the reaction of ketones II and III with Grignard reagents,[14] it being observed that both ketones react extremely slowly with the latter reagents in comparison with the addition of methylmagnesium bromide to methoxy estrone.[15] Such a behaviour can again be understood in terms of resistance to attack on the carbonyl group from both sides of the molecule.

In order to circumvent the unfavourable distribution of isomers in the reduction mixture from I, the tosyl ketone was first reduced with sodium borohydride to yield a single isomer of the C-17 alcohol IV, presumably with β- OH orientation, which could be further catalytically reduced to the 14α- alcohol V in 73% yield. An NMR spectrum of the crude reaction product from the last reduction indicated the presence of small amounts of the 14β- isomer of V. Oppenauer oxidation of V with aluminium isopropoxide and cyclohexanone conveniently afforded ketone II. Conversion of II to 6-aza-equilenin methyl ether (VI) was achieved by refluxing it with 80% sulphuric acid and a trace of arsenic pentoxide, albeit in low yields. A more attractive approach to VI proved to be via the tosyl alcohol V. The latter alcohol readily underwent an oxidative detosylation upon treatment with sodium hydride, to form the quinoline derivative VII in excellent yield (85%). The same product was also obtained upon refluxing tosyl ketone II with LAH in tetrahydrofuran. Oppenauer oxidation of VII gave a sample of the aza-equilenin ether (VI) which was identical to the one obtained upon acid catalysed detosylation of II in presence of arsenic pentoxide. Demethylation of VI with pyridine and hydrochloric acid resulted in the formation of 6-aza-equilenin (VIII).

Careful chromatography of the reaction products obtained upon treatment of V with sodium hydride showed the presence of significant amounts of a second compound which has been recognized as alcohol IX. The base-catalyzed oxidative detosylation of V can be readily understood in terms of a C-7 proton abstraction followed by an N-S bond cleavage. This mechanism is reminiscent of related detosylation reactions observed in the pyrrole and azepine systems.[16] Considerable driving force for such a process would be derived from the aromatization reaction resulting in the quinoline nucleus. The unexpected formation of the tetrahydroquinoline derivative (IX), however, requires the involvement of a second pathway. Mechanistically, the initiation of the latter reaction may be visualized as the consequence of a hydride addition at C-8. Subsequent loss of the sulphinate ion from the system may

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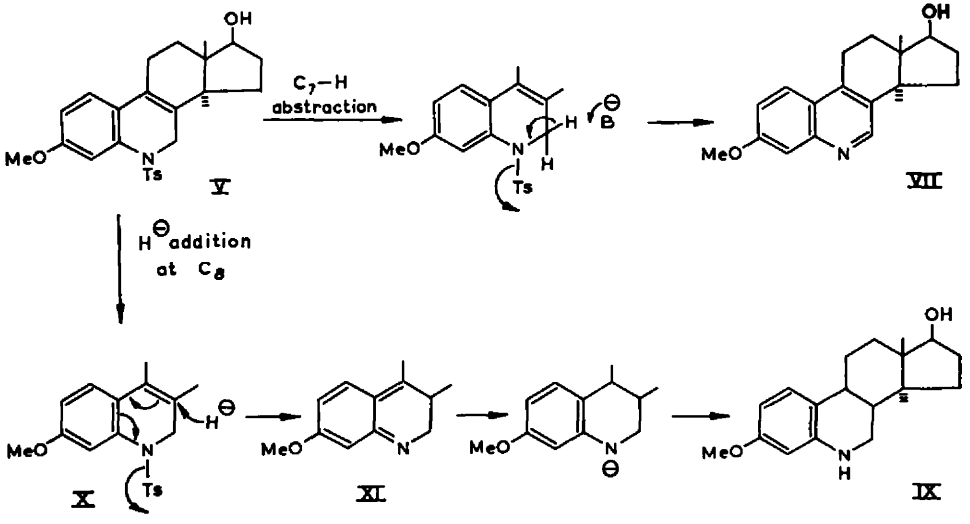
[13] The molecular model indicates a strong steric interaction to the disposition of the tosyl group and the C_{18}-methyl substituent on the same side of the steroidal plane.

[14] Ketone II was converted into the corresponding C_{17}-methyl-C_{17}-hydroxy compound by refluxing it with MeMgBr in THF for 48 h. In the crude reaction product only a small quantity of the starting material was detected from its IR spectrum. Under the same conditions the reaction of ketone III with MeMgBr was even slower, the largest part of the starting ketone being recovered.

[15] C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **76**, 4092 (1954).

[16] [a] G. Ege, *Tetrahedron Letters* 1665 (1963); [b] G. R. Proctor, *Chem. & Ind.* 408 (1960).

occur in a separate step or via the mediation of the concerted process X. Reduction of the resulting unsaturated imine intermediate (XI) by a second hydride addition at C-9, followed by protonation, would eventually lead to the formation of alcohol IX.



When ketone II was treated with a calculated amount of potassium metal in liquid ammonia at —80°, and under conditions of slow stirring, the predominant product of the reaction was 6-aza-equilenin methyl ether (VI); in addition, small quantities of the corresponding alcohol (VII) and the 6-aza-estradiol derivative (IX) were also formed. If, instead, a two- to three-fold excess of potassium was employed and the addition carried out rapidly with vigorous stirring, a mixture was obtained from which about 30% of IX could be isolated after chromatographic separation. A further increase in the ratio of potassium to ketone, however, only resulted in a considerable lowering of the total yield of the products. Although definite details regarding the mechanism of reduction of II with potassium and liquid ammonia are lacking, some comments may be pertinent. In a separate experiment it was possible to demonstrate that under conditions of the reduction the 6-aza-equilenin ether (VI) does not lead to alcohol IX. Thus, the reaction with metal and ammonia is similar to that observed with the metal hydrides in displaying the aromatization and reduction reactions as competitive processes.

The formation of the 6-aza-estradiol-3-methyl ether (IX) most probably proceeds via the intermediacy of ion XII in a manner analogous to that described for the reduction of styrenoid bonds of several steroidal systems,[17] and, presumably with the same stereochemical consequences.[18] Compound XII itself can be produced either by a direct base-catalysed fission of the N-Ts bond in II or by an concerted sulphinate ion elimination following electron addition at the C_8-C_9 double bond. Since the electron addition steps may be expected to be relatively sensitive to the concentration

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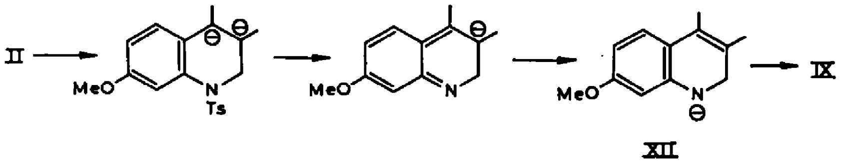
[17] [a] W. S. Johnson, A. D. Kemp, R. Pappo. J. Ackerman and W. F. Johns, *J. Amer. Chem. Soc.* 78, 6312 (1956); [b] G. A. Hughes and H. Smith, *Proc. Chem. Soc.* 74 (1960).

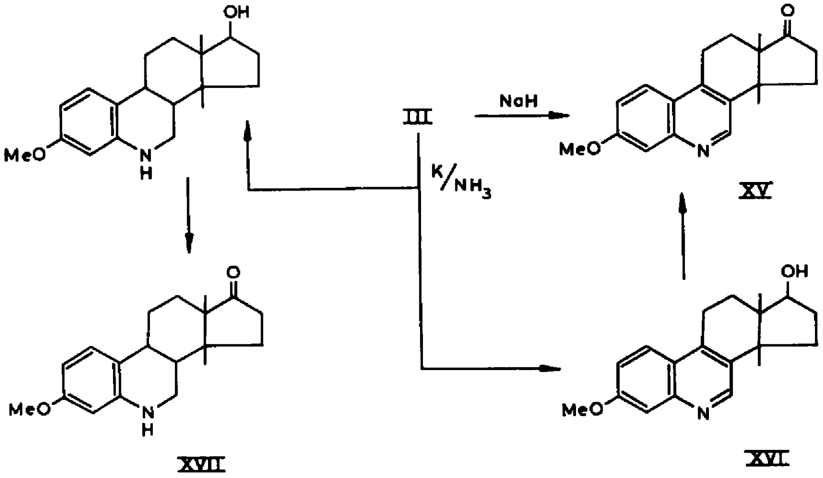
[18] For a discussion of the stereochemical factors involved see H. Smith, *Organic reactions in liquid ammonia* Vol. 1 part 2; p. 228, J. Wiley, New York (1962).

of the "free electrons" in the medium, the observed requirement of an optimum concentration of the metal would appear to support the mechanism involving such a step.



Direct Oppenauer oxidation of the reaction mixture obtained upon treatment of II with potassium and ammonia, followed by extensive chromatography, afforded ketone XIII in an overall yield of 20%. Demethylation of XIII yielded a slightly coloured product the spectral properties of which were in agreement with XIV. Attempts at purification of XIV were unsuccessful in view of its rapid deterioration, which behaviour is in accordance with its proposed aminophenol structure.

The 14β-isomers of the estrogens were prepared from tosyl ketone III in an analogous manner. Treatment of III with sodium hydride gave a mixture containing only a small amount of 6-aza-14β-equilenin methyl ether (XV). However, a similar reaction with the corresponding C_{17}-alcohol afforded XVI in reasonable yield. Reaction of III with potassium and liquid ammonia again resulted in a mixture of 6-aza-isoequilenin and 6-aza-isoestrone derivatives. Oxidation of the mixture with aluminium isopropoxide and cyclohexanone followed by chromatography of the products yielded the two ketones (XV and XVII).



Stereochemistry

The stereochemical assignments of the C/D ring junction in the tosyl ketones II and III have been based on the positions of the C-18 methyl resonance in their NMR spectra. The extension of these assignments to the corresponding aza-equilenin ethers (VI and XV) which in the first instance seems amply justifiable in view of the reactions leading from II and III to their formation, also finds its confirmation in the

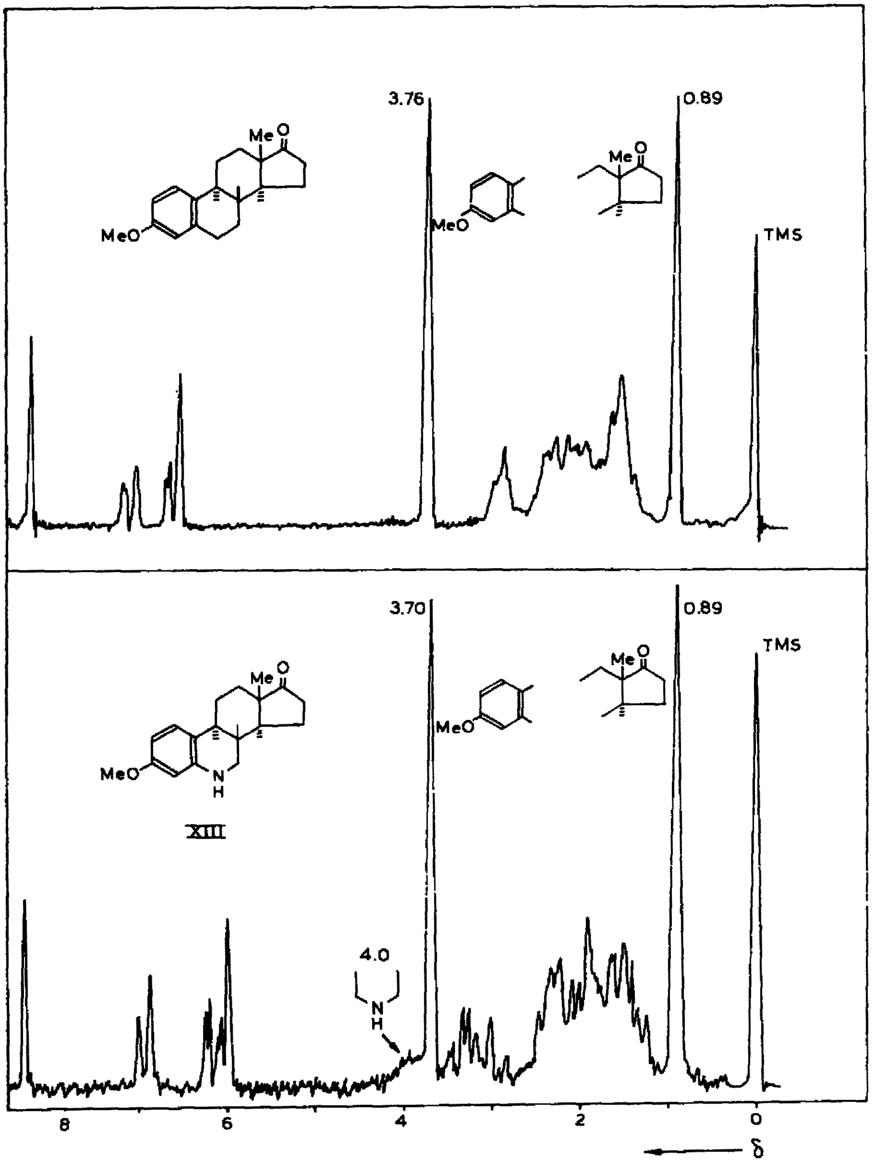


FIG. 1.

NMR spectra of these substances. As expected, the field associated with the ring current of the aromatic ring B causes a diamagnetic shift of the C-18 methyl group in the 14α-isomer (VI).[11] Resonance values for the angular methyl groups of VI and XV being 0·75 ppm and 1·07 ppm respectively. Further, the mass spectra of the two isomers[1] are characteristic in their fragmentation patterns and, what is more significant, are closely related to the spectra of the *normal* 14α- and 14β-equilenin methyl ethers.[19]

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[19] C. Djerassi, J. M. Wilson, H. Budzikiewicz and J. W. Chamberlin, *J. Amer. Chem. Soc.* **84**, 4549 (1962).

A detailed discussion of these spectra is presented elsewhere.[1] Some conclusions concerning the stereochemistry of the aza-estrone system (XIII) may also be drawn. Since the reactions involved in the transformation of II to XIII are not expected to affect the nature of the C/D ring junction the latter may be assumed to possess a *trans* configuration in XIII. Steric assignments for the hydrogens at C-8 and C-9 are, however, more difficult. If the stereochemical considerations which play a decisive role in the metal-ammonia reduction of the analogous carbocyclic system[18] are also operative in the present case, then the predominant product, which is isolated, should possess the 8β, 9α-configuration. Support for the latter stereochemistry of XIII is derived from its NMR spectrum which bears remarkable resemblance in the appropriate regions to that of estrone methyl ether (Fig. 1). A similar argument has been recently employed in making the stereochemical assignments for the C-8 and C-9 protons in 11-aza-progestrone.[20] The mass spectrum of XIII (Fig. 2) also displays an overall fragmentation pattern which is analogous to that reported for estrone methyl ether,[21] although a comparison of the intensity of the fragments indicates that the facile decomposition of 6-aza-estrone which leads to the formation of the aromatic ion XVIII subordinates the prominence of the other fragments in its spectrum. While

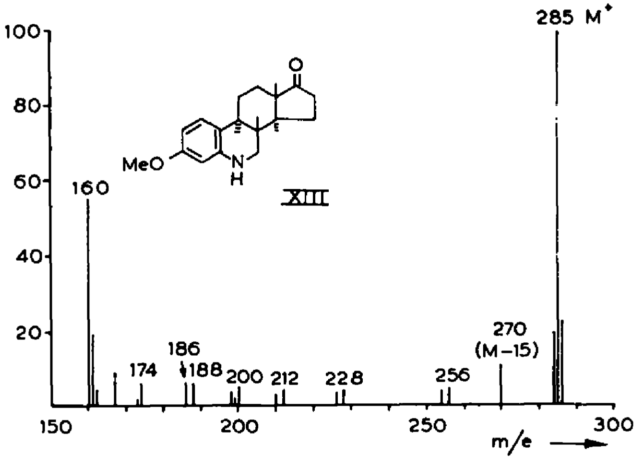
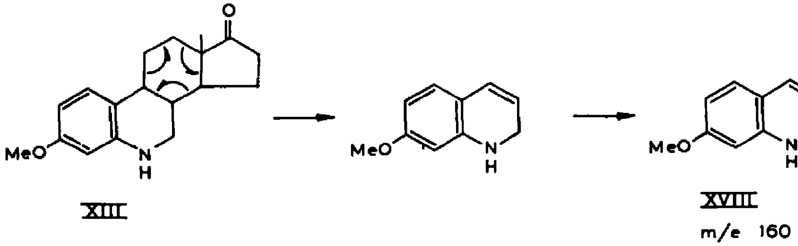


FIG. 2.



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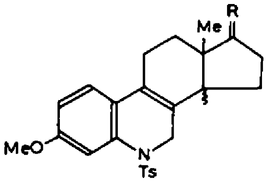
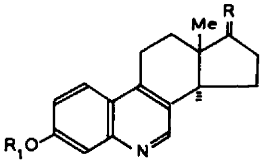
[20] J. P. Kutney and I. J. Vlattas, *Steroids* 4, 595 (1964).

[21] Ref. 19, p. 4545.

an unequivocal decision regarding the stereochemistry of XIII is not possible at the present time, since no substances are available for reference, we do however feel that in the light of the NMR and mass spectral evidence a tentative assignment can be made in favour of the 8β, 9α, 14α-configuration for XIII. The results of preliminary biological tests are collected in Fig. 3. Results are taken from standard tests in which a dose of 2 mg/kg weight was employed.

		I	II	III	IV	V	VI
Oestrogenic		–	±	–		+	
Stim.–Oestrogenic		–	–	–	–	–	–
Uterotropic		±	–	+	+	+	+
Anti–Uterotropic		–	–	±	+	–	–
Par.–Progestational	200 γ	–	–		–		–





I R = O 14α
II R = O 14β
III R = $<^{OH}_{H}$ 14α

IV R = O, R$_1$ = Me
V R = $<^{OH}_{H}$, R$_1$ = Me
VI R = O, R$_1$ = H

FIG. 3.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were measured in KBr pellets and were determined on a Perkin-Elmer Model 125 spectrophotometer. UV spectra were determined on a Zeiss RPQ 20 automatic recording spectrophotometer and the NMR spectra on a Varian HR 60 spectrometer, with tetramethylsilane (TMS) as an internal reference. All NMR spectra were taken in $CDCl_3$ as a solvent and chemical shifts are described in ppm from TMS. The UV spectra were measured in ethanolic solution.

(±)-*N-Tosyl-6-aza-8-dehydroestrone methyl ether* (II)

Hydrogenation of ketone I (23·0 g) in 500 ml THF* over 46·0 g (2%) Pd-$CaCO_3$ afforded, after an uptake of 1283 ml H_2 (calc. 1267 ml) and work-up, an oil which gave by fractional crystallization from THF-MeOH (1:3) 5·4 g of II, m.p. 208–210°. From the mother liquor an additional 0·6 g was obtained, total yield 6·0 g (26%). (Found: C, 68·7; H, 6·4; N, 3·2; S, 7·5; $C_{26}H_{27}NO_4S$ requires: C, 68·63; H, 6·22; N, 3·20; S, 7·34%). The IR spectrum showed a carbonyl absorption at 1735 cm^{-1} while UV maxima were found at 223 (ε = 20·000), 241 (ε = 21·800) and 280 (ε = 12·300) nm. The $C_{18}CH_3$ absorption in the NMR spectrum was at 0·60. From the combined mother liquors remaining after isolation of II, 8·0 g (34%) of III was obtained, which was recrystallized from THF—MeOH (1:10), m.p. 129–131°. (Found: C, 68·7; H, 6·2; N, 3·2; S, 7·4; $C_{26}H_{27}NO_4S$ requires: C, 68·63; H, 6·22; N, 3·20; S, 7·34%). Carbonyl absorption in IR spectrum was at 1729 cm^{-1} and UV maxima were found at 225 (ε = 20·600), 240 (ε = 23·000) and 274 (ε = 12·000) nm. NMR spectrum showed singlets at 0·84 ($C_{18}CH_3$), 2·29 ($PhCH_3$) and 3·81 ($PhOCH_3$).

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* Tetrahydrofuran is abbreviated as THF.

The ketone II was also obtained by Oppenauer oxidation of V. After refluxing a mixture of 0·60 g V, 0·5 ml cyclohexanone and 0·85 g aluminium isopropoxide in 30 ml toluene for 3 h, the solution was cooled, 200 ml ether added and the mixture washed with KOH aq (5%), water and sat. NaCl aq. After evaporating the solvent the residue was crystallized from THF—MeOH, yield 0·28 g (47%)

(±)-*N-Tosyl-6-aza-bisdehydro-8, 14-estradiol methyl ether-3* (IV)

Sodium borohydride (5·60 g) was added to a mixture of I (11·20 g), 300 ml EtOH and 20 ml water. The solid ketone gradually dissolved while later on the solution became turbid and finally solidified. After 20 h at room temp the mixture was cooled, 17 g acetic acid was slowly added and the solution concentrated to ⅓ of its original volume. The residue was diluted with 600 ml water and the alcohol extracted with 600 ml THF—ether (1:3). The organic layer was washed with $NaHCO_3$ aq, water and finally NaCl aq and dried ($MgSO_4$). After recrystallizing the product from THF—MeOH, the yield was 9·30 g (83%). The mother liquor afforded a second crop of the alcohol (0·9 g). m.p. 178–179°. (Found: C, 68·5; H, 6·6; N, 3·4; S, 7·4; $C_{25}H_{27}NO_4S$ requires: C, 68·63; H, 6·22; N, 3·20; S, 7·34%.) Strong IR absorption at 3558 cm^{-1} indicated the presence of an hydroxy group; UV maxima were at 254 (ε = 17·300) and 316 (ε = 18·100) nm.

(±)-*N-Tosyl-6-aza-8-dehydro-estradiol methyl ether-3* (V)

The alcohol IV (7·70 g) in 140 ml of THF was hydrogenated over 15 g Pd-$CaCO_3$ the mixture filtered and the catalyst extracted with hot THF. Concentration of the combined solutions yielded an oil, from which on crystallizing from THF—MeOH (1:2) 5·65 g (73%) of V was obtained, m.p. 199–202°. (Found: C, 68·0; H, 6·6; N, 3·3; S, 7·3; $C_{25}H_{29}NO_4S$ requires: C, 68·29; H, 6·65; N, 3·19; S, 7·29%.) Hydroxyl absorption in the IR spectrum was found at 3544 cm^{-1} and UV maxima at 226 (ε = 20·600), 241 (ε = 23·700) and 279 (ε = 15·300) nm. In the NMR spectrum the $C_{18}CH_3$ absorbed at 0·49.

(±)-3-*Methoxy-6-aza-17β-hydroxy-estra*-1, 3, 5(10), 6, 8-*pentaene* (VII)

The alcohol V (0·50 g) was dissolved in 50 ml dry THF and to the resulting solution 2·0 g NaH (50% oil dispersion) was added. After stirring and refluxing the mixture for 18 h under N_2, the excess of hydride was decomposed with water and the aquous solution extracted with ether. After extracting the ether with HCl, the acid solutions were neutralized with KOH aq (10%) and the precipitate dissolved in ether. The latter solution afforded after washing with water and sat NaCl aq followed by evaporation of the solvent, the equilenin alcohol (VII). Recrystallization from MeOH gave 0·27 g (80%) of the pure product, m.p. 188–189°. (Found: C, 76·0; H, 7·6; N, 4·8; $C_{18}H_{21}O_2N$ requires: C, 76·29; H, 7·47; N, 4·94%). The NMR spectrum showed a singlet ($C_{18}CH_3$) at 0·67 and in the UV spectrum the following maxima were measured: 215 (ε = 26·000). 235 (ε = 45·000), 256 (ε = 4·350), 327 (ε = 4·700) and 339 (ε = 5·100) nm.

Upon chromatography of the mother liquors a small quantity of the 6-aza-estradiol methyl ether-3 (IX) was isolated.

(±) *6-Aza-equilenin methyl ether* (VI)

a. *Via Oppenauer oxidation of* VII. A mixture of 1·0 g of VII, 80 ml dry toluene, 2·3 g aluminium isopropoxide and 1·3 ml cyclohexanone was stirred under reflux for 4 h. After cooling, ether was added and the solution washed several times with KOH aq, water and HCl aq (4%). After neutralization of the acid solution and dissolving the precipitate in ether, the organic layer was washed with water and NaCl aq. Evaporation afforded 0·98 g of an oil which was chromatographed over aluminium oxide. Elution with cyclohexane—ethyl acetate (4:1) gave 0·1 g (11%) 6-aza-equilenin methyl ether and 0·4 g starting alcohol (VII). The ketone was recrystallized from ether—THF, m.p. 180–182°. (Found: C, 76·6; H, 6·9; N, 5·1; $C_{18}H_{19}O_2N$ requires: C, 76·84; H, 6·81; N, 4·98%). The carbonyl absorption in the IR spectrum was at 1735 cm^{-1}, UV maxima were found at 236 (ε = 44·500), 258 (ε = 4·650), 290 (ε = 2·950), 328 (ε = 5·200) and 340 (ε = 5·500) nm. The $C_{18}CH_3$ absorption in the NMR spectrum was found at 0·75.

b. *Via reduction of ketone* (II) *with potassium in liquid ammonia.* Ketone II (3·50 g) was dissolved in a mixture of 200 ml THF and 300 ml ammonia. After cooling the solution to −80° 2·0 g K, cut into pieces of 0·2 g, were added over a period of 3 h. Decomposition of the excess K, with 10 g NH_4Cl, followed by evaporation of the ammonia gave a residue which was dissolved in ether. After extracting the ether layer with dil. HCl aq and neutralizing the latter solution with KOH, the precipitate formed was taken up into ether once again. Finally, after washing the ether solution with water and sat NaCl aq, followed by evaporation of the solvent, 2·0 g of an oil was obtained. Chromatography over florisil with a mixture of cyclohexane—ethyl-acetate (4:1), yielded 0·94 g (40%) 6-aza-equilenin methyl ether.

(±) *6-Aza-equilenin* (VIII)

A mixture of 0·39 g methyl ether (VI) and 8·0 g freshly prepared pyridine hydrochloride was stirred under N_2 for 40 min at 235°. Decomposition of the brown melt with ether followed by acidification with HCl aq (38%) till pH = 6 gave a precipitate which was dissolved in a mixture of THF and ether. After washing the latter solution with water and sat. NaCl aq and evaporating the solvent, 0·25 g (65%) 6-aza-equilenin was obtained. After recrystallization from ether—THF the product melted at 258–260°. (Found: C, 75·8; H, 6·5; N, 5·0; $C_{17}H_{17}O_2N$ requires: C, 76·38; H, 6·41; N, 5·24%.) The IR spectrum showed bands at 3360 cm^{-1} and 1729 cm^{-1}, which were assigned respectively to the phenolic OH and the carbonyl absorption.

(±) *6-Aza-estradiol methyl ether* (IX)

Ketone II (2·4 g) was dissolved in a mixture of THF (180 ml) and ammonia (300 ml). After cooling the mixture to −80°, 3·4 g K were added under vigorous stirring in 30 min. After completion of the reaction (2·5 h) the ammonia was evaporated and the residue worked up in a manner already described; 1·1 g of the oily residue were chromatographed over a florisil column. Elution with a mixture of cyclohexane—ethyl acetate (19:1) afforded 0·32 g IX. After crystallization from a mixture of cyclohexane—ethyl acetate, the alcohol had a m.p. of 178–179°. (Found: C, 74·9; H, 8·8; N, 4·9; $C_{18}H_{25}O_2N$ requires: C, 75·22; H, 8·77; N, 4·87%.) In the IR spectrum sharp absorptions were present at 3478 cm^{-1} (OH) and 3350 cm^{-1} (NH); the UV maxima were at 214 (ε = 27·000), 251(ε = 7·300) and 299 (ε = 4·000) nm. Further elution with cyclohexane—ethyl acetate (4:1) yielded 0·33 g 6-aza equilenin alcohol (VII).

(±) *6-Aza-estrone methyl ether* (XIII)

After reduction of 2·11 g II via the procedure outlined above, the resulting oil was dissolved in 100 ml dry toluene. To this solution 4·4 g aluminium isopropoxide and 3 ml cyclohexanone were added. Upon refluxing for 4 h and working up in the usual manner, 1·0 g of an oil was obtained which, after chromatography over florisil and elution with cyclohexane—ethyl acetate (19:1), yielded 0·24 g (17·3%) 6-aza-estrone methyl ether (XIII), together with a small amount of IX. m.p. 164–166°. (Found: C, 75·6; H, 8·3; N, 4·7; $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; N, 4·91%.) The IR spectrum had absorptions at 3380 cm^{-1} (NH) and 1719 cm^{-1} (C=O) and maxima in the UV were found at 214 (ε = 27·000), 251 (ε = 7·300) and 299 (ε = 4·000) nm. The position of the $C_{18}CH_3$ signal in the NMR spectrum was at 0·89.

Further elution with cyclohexane—ethyl acetate (4:1) gave 0·25 g 6-aza-equilenin methyl ether(VI).

The ether XIII (0·03 g) was demethylated via the procedure used for demethylation of the equilenin methyl ether. Neither through crystallization, nor via chromatography it was possible to purify the crude reaction product. m.p. 181–185°. In the IR spectrum absorptions were found at 1726 cm^{-1} (C=O) and from 3200–3450 cm^{-1} (OH-NH).

(±) *6-Aza-14β-equilenin methyl ether* (XV)

To 3·5 g ketone III, dissolved in a mixture of 150 ml THF and 300 ml ammonia, 5·0 g K were added in 1 h, at −80°, under vigorous stirring. After another 75 min the excess amide was decomposed with 10 g NH_4Cl. Working up the reaction mixture via the procedure described above, afforded 2·21 g of an oil, which was chromatographed over 55 g florisil. Elution with mixtures of cyclohexane-ethyl acetate (respectively 19:1 and 4:1) afforded an oil (0·79 g) which mainly consisted of the 14β-estradiol methyl ether, and two crystalline products, the structures of which were established as alcohol XVI (0·40 g) and the corresponding ketone (XV). The latter compound was recrystallized from THF-ether (1:1) to yield pure 6-aza-14β-equilenin methyl ether, m.p. 134–135°. (Found: C, 76·7; H, 6·8; N, 5·1; $C_{18}H_{19}O_2N$ requires: C, 76·84; H, 6·81; N, 4·98%.) The carbonyl absorption in the IR spectrum was at 1725 cm^{-1} and in the UV spectrum maxima were found at 236 (ε = 55·500), 276 (ε = 3·600), 325 (ε = 4·600) and 337 (ε = 4·900) nm. The $C_{18}CH_3$ absorption in the NMR spectrum was at 1·07.

The alcohol (XVI) was recrystallized from THF–ether (1:1), m.p. 178-180°. The IR spectrum had a strong absorption at 3340 cm^{-1}.

(±) *6-Aza-14β-estrone methyl ether* (XVII)

The oil obtained in the chromatography of the reaction product of the potassium-ammonia reduction of ketone III, was dissolved in 70 ml dry toluene and treated with 2·2 g aluminium isopropoxide and 2·4 ml cyclohexanone. The mixture was refluxed for 5 h. Working up in the usual way afforded an oil, which was chromatographed on florisil. Elution with 1100 ml of cyclohexane–ethyl acetate (19:1) gave 0·049 g of 6-aza-14β-estrone methyl ether, which was recrystallized from MeOH, m.p. 136·5-137·5°. (Found: C, 75·6; H, 8·2; N, 4·6; $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; N, 4·91%.) Absorptions at 3380 cm^{-1} (NH) and 1731 cm^{-1} (C=O) were found in the IR spectrum, while maxima in the UV spectrum were at 213 (ε = 25·500), 250 (ε = 5·850) and 301 (ε = 3·900) nm. The $C_{18}CH_3$ singlet in the NMR spectrum was at 1·03.

The 6-aza-14β-estradiol methyl ether, which was also obtained on chromatography, had after recrystallization from THF–ether a m.p. of 156-157°.

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