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HETEROCYCLIC STEROIDS—XIII[1]

THE SYNTHESIS OF N-METHYL-6-AZA-8(14)-DEHYDRO-19-NOR-TESTOSTERONE

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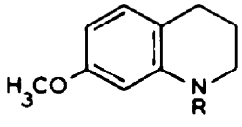
Abstract—Lithium–ammonia reduction of 1,2,3,4-tetrahydro-7-methoxyquinolines **1** and **2** gives the corresponding octahydroquinolines **5** and **6**. Some aspects of the reaction pathway are discussed. The method has been applied for the reduction of the 8,14-dehydro-6-aza-estrone derivative **11**, which affords the 19-nor-testosterone analogue **14**

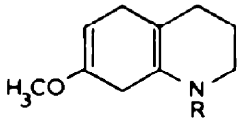
FOLLOWING the development of a facile synthetic route for construction of the 6-aza-estrone skeleton, elaboration of the scheme to obtain the 19-nor-6-androstane system was considered. A potential approach for the achievement of this goal consists in the metal-ammonia reduction of ring A to the corresponding dihydro derivative followed by hydrolysis to the 4-dehydro-3-keto system.

Although ample information is available on the metal-ammonia reduction of phenolic ethers,[3] only a few cases have been reported in which a ring substituted amino ether have been successfully converted into its dihydro derivative.[4]

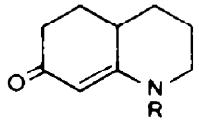
To investigate the general behaviour of aminophenyl ethers, initial studies were carried out on model systems. Tetrahydroquinolines **1** and **2** were chosen for this purpose. Both compounds were synthesized via the hydrazine–potassium hydroxide treatment of the corresponding dihydroquinolones.[5]



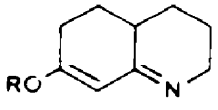
1 R = CH_3
2 R = H



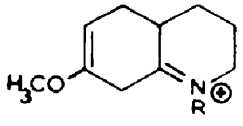
3 R = CH_3
4 R = H



5 R = CH_3
6 R = H



7 R = CH_3
8 R = H



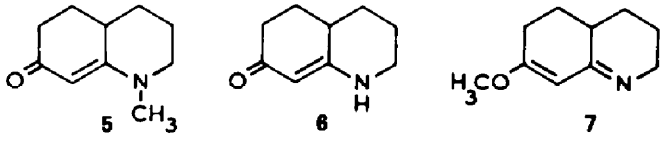
9 R = CH_3
10 R = H

Reduction of the aromatic ring of quinoline **1** with lithium and ethanol in ammonia gave a mixture of the starting material and enol ether **3**. Considerable improvement in the yield of the enol ether was achieved by carrying out the reaction with lithium and ethanol in methylamine. Distillation of the crude reaction product afforded

the pure compound in 72% yield. Its NMR spectrum showed Me singlets at δ 2·64 (CO—Me) and δ 3·48 (N—Me), a 2-proton singlet for C_8 methylene protons at δ 2·53 and a diffused singlet at δ 4·50 for the C_6 olefinic proton. Shaking with water converted ether **3** into the enamine ketone **5**, which after crystallization from ether-hexane had a m.p. of 79–80°.[6]

The NMR characteristics were: δ 2·86 singlet (N—Me) and δ 5·06 singlet (vinylic H), Attempted hydrolysis of **3** in weak acidic medium resulted in extensive decomposition, presumably via acid catalysed ring opening of the enamine system.

Reduction of quinoline **2** with lithium and ethanol in methylamine gave a mixture of two products, the enol enamine **4** and the imine **7**. Structure proof of the products was based on their spectral characteristics. IR spectrum exhibited typical absorptions at 1670 and 1700 cm^{-1} for the enamine **4** and an additional strong absorption at 1635 cm^{-1} for the imine **7**. Either distillation of the crude reaction mixture, or treatment with water rearranged enamine **4** into the imine **7** without further affecting the molecule. The absence of any ketonic material in the latter reaction may be partly due to the increased stability of enol imine system **7** in which initial protonation



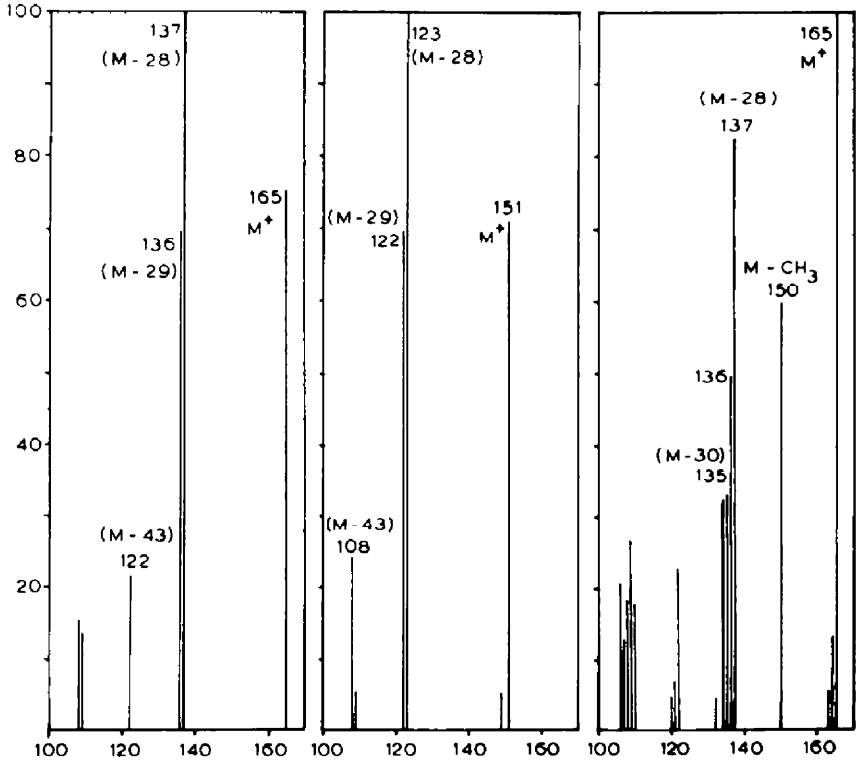


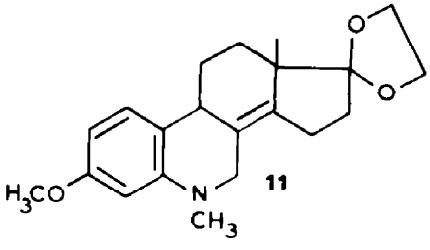
FIG. 1

occurs on the N atom. The enol imine displayed NMR absorptions at δ 3·64 (s, OMe) and δ 5·23 (s, C=C—H). Prolonged refluxing of imine **7** with 2N HCl gave the crystalline enamine ketone **6**, for which in principle two tauteromeric structures are possible.[7] However, from the similarity of its UV spectrum with the corresponding spectrum of N—Me ketone **5** a major contribution of the imine form **8**, in neutral solution, can be excluded.

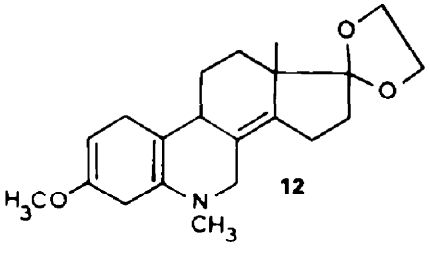
That indeed the ketone form **6** predominates is strongly suggested by a comparison of the mass spectra of compounds **5**, **6** and **7**. The closely related pattern of the spectra of ketones **5** and **6** is reminiscent of the fragmentation pathways of piperidines and octalones,[8] on the other hand, the spectrum of the enol imine shows an entirely different picture. Significant features being the increased stability of the molecular ion peak *vs* the M-28$^+$ ion and the presence of a conspicuous M-15$^+$ ion, which is absent in the spectrum of the ketone **5**. (Fig. 1).

Finally it may be noted that the NMR spectra of enamine ketones **5** and **6** are superimposable and, bear no resemblance to the spectrum of imine **7**. From these spectral data it is concluded that under neutral conditions the keto enamine form is the preferred one for compounds **5** and **6**.

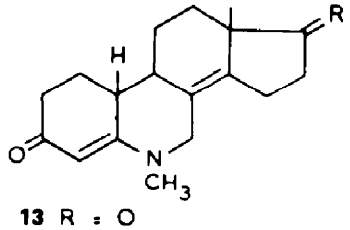
The observed differences in the hydrolytic behaviour of enol ethers **3** and **4** deserve some comment. In neutral solution protonation and isomerization will give rise to the conjugated iminium forms **9** and **10**, which only differ in the substituent at the N atom. While it is obvious that **10** can stabilize itself via rapid loss of a proton, such a possibility is not available to **9**; which, however, can split off the O-alkyl substituent, at a slower rate, to form the enamine ketone **5**. Dealkylation of **10** in acid solution would occur via the same mechanism, the enhanced rate being due to the higher concentration of the species. A second point which can also be explained on the basis of intermediates **9** and **10** is the observed difference in stability of enamine ketones **5** and **6**. Addition of a proton to **6** results in a reversible process, while a similar reaction with ketone **5** leads to the iminium salt, which ultimately decomposes by further reaction with water.



11

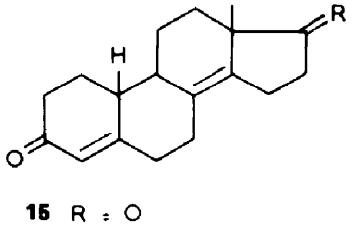


12



13 R = O

14 R = H, OH



15 R = O

16 R = H, OH

Application of the reduction procedure to aza-estrone derivative **11** gave the dihydro derivative **12** in good yield. Surprisingly, no reduction was observed when the reaction was carried out in ammonia. This may be partly due to the low solubility of the compound; significantly however, application of the procedure of Dryden,[9] which works in the case of estrone, also failed.

Enolether **12** could not be readily hydrolysed by merely shaking with water. Brief acid treatment gave ketone **13** as a brown syrup which was purified via column chromatography. Particularly relevant to its structure proof was its NMR spectrum (Fig. 2) in which the vinylic hydrogen was observed at δ 5·17 ppm.

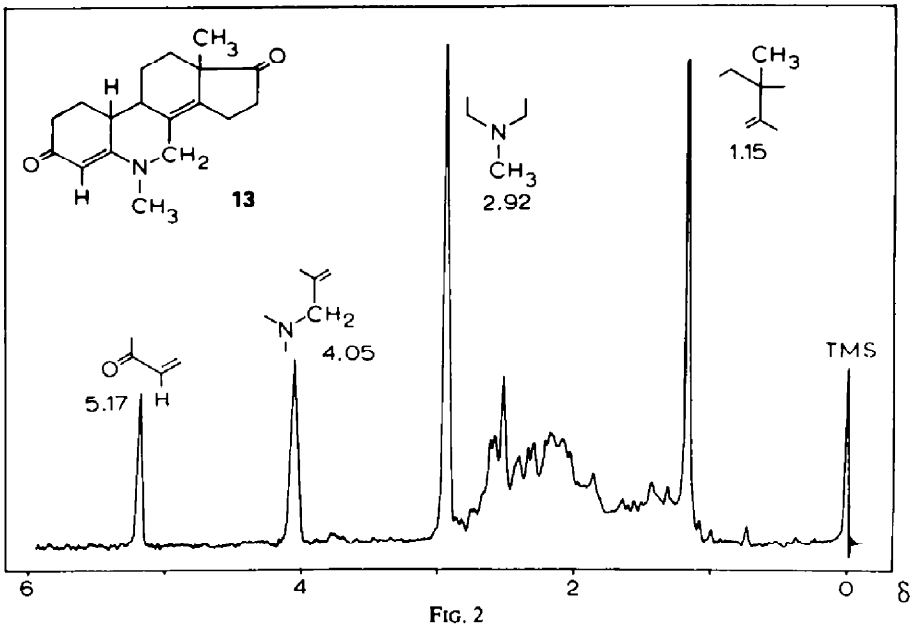


FIG. 2

Although an unequivocal proof for the stereochemical assignment at C_9 and C_{10} in **13** is not available at this stage, our reasons for allocation of the 9α, 10β configuration are based on the following arguments: reduction of estrone under equilibrating conditions is known to proceed stereoselectively, with exclusive formation of the thermodynamically more stable 10β-H isomer; also in the reduction of the 6-aza ketal **11** only a single isomer was obtained in high yield and no second isomer could be detected. Pertinent to the argument is a comparison of the NMR spectra of heterocyclic steroids **13** and **14** with their carbocyclic analogues **15** and **16**. In spite of the expected difference caused by variation of the chemical environment the close agreement of the C_{18}—Me absorptions in these compounds—1·15 and 0·97 ppm for **13** and **14**, and 1·14 and 0·97[11] for **15** and **16**—provides further evidence for the 9α, 10β geometry.*

* Although the position of the C_{18}—Me absorption in general does not provide an unique proof for the C_9–C_{10} configuration (9β, 10α isomers having similar chemical shifts as compared to 9α, 10β steroids) the *syn* and *anti* relationships of C_9 and C_{10} protons are characterized by differences of 0·07 (C_{17}—OH) and 0·09 (C_{17}, CO) ppm in the chemical shift of the C_{18} Me signal.[13] Since we have assigned the C_9—α-H configuration to the starting ketal **11**, the attribution of a C_9—α-H, C_{10}—β-H geometry in the reduced system is the logical extension of this reasoning.

Sodium borohydride reduction in methanol at 0° afforded the C_{17} alcohol in 80% yield. As could be expected from the known behaviour of β-acylenamines no reduction of the C_3–carbonyl group occurred.[12] Alcohol **14** was far less stable in comparison with its ketonic precursor **13**, column chromatography resulted in complete destruction of the molecule. Similar behaviour upon chromatography has also been observed in the case of the ring A aromatic analogue.[1]

The fact that only one stereoisomer was isolated is in accordance with the expected stereochemical reduction course and provides strong evidence for a β-configuration of the C_{17}—OH.

EXPERIMENTAL

All m.ps 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-2 mass spectrometer.

1 *Methyl-7-methoxy*-1,2,3,4-*tetrahydro-quinoline*. **1**. A mixture of 9·85 g 1 methyl-1,2,3,4-tetrahydro-4-oxo-7-methoxy-quinoline,[1] 100 g KOH. 200 ml hydrazine monohydrate and 500 ml diethylene glycol, was heated for 5 hr at 190°.

After dilution with 3 l. water the soln was extracted with benzene and the organic fraction washed with water and sat. NaCl aq. Evaporation of the solvent and distillation of the residue afforded 6·7 g of colorless liquid, b.p. 90–100°/0·4 mm Hg, n_D^{20} = 1·5760; UV maxima at 214 (26,000), 257 (6300) and 301 (3150) nm. Methiodide, m.p. 172–173°. (Found: C, 45·0; H, 5·7; N, 4·4; I, 39·2. $C_{12}H_{18}NOI$ requires: C, 45·15; H, 5·68; N, 4·38; I, 39·75%).

1,2,3,4-*Tetrahydro-7-methoxy-quinoline* **2**. A mixture of 18 g 1,2,3,4-tetrahydro-4-oxo-7-methoxy-quinoline, 830 ml diethyleneglycol and 330 ml hydrazine hydrate was stirred for 1 hr at 130°, after which 180 g KOH were added and the soln heated for 8 hr at 170°. After dilution with 4 l. water and extraction with benzene, the organic fraction was washed with water and sat. NaCl aq and the solvent evaporated. Distillation afforded 13·6 g of **2**, b.p. 98–102°/0·1 mm Hg, n_D^{20} = 1·5879; UV maxima at 214 (23,900), 250 (6400) and 299 (3100) nm. NMR: δ 1·87 quintet (β-CH_2), 2·68 triplet (γ-CH_2), 3·23 triplet (α-CH_2) and 3·69 singlet (OMe) ppm. M.p. of HCl salt 190–191°. (Found: C, 60·4; H, 7·0; N, 7·0; O, 8·2; Cl, 17·7. $C_{10}H_{14}NOCl$ requires: C, 60·15; H, 7·07; N, 7·02; O, 8·01; Cl, 17·76%).

1-*Methyl*-1,2,3,4,5,8-*hexahydro-7-methoxy-quinoline* **3**. 0·12 g of Li were added at −35° to a soln of 1 g of **1** in 30 ml methylamine and 1·15 ml EtOH. After disappearance of the blue color (5 min), the methylamine was evaporated, 10 ml water added to the chilled mixture, and extracted with ether. The ether layer was washed with sat. NaCl aq, dried over $MgSO_4$ and finally distilled, which afforded 0·73 g of **3**, b.p. 70–85°/0·1 mm Hg, n_D^{20} = 1·5354; NMR (CCl_4) δ: 2·53 singlet (α-CH_2); 2·64 singlet (N—Me); 3·48 singlet (OMe), 4·50 diffused singlet (=CH) ppm.

2,3,4,4*a*,5,6-*Hexahydro-7-methoxy-quinoline* **7**. 1·48 g of Li wire was added in portions to a mixture of 11·38 g of **2**, 14·3 ml EtOH and 330 ml methylamine at −35°. After disappearance of the blue color, the reaction mixture was worked up as usual, yield: 9·2 g of an oil, b.p. 85–100°/0·2 mm Hg, which slowly solidified, m.p. 38–40°. (Found: C, 72·1; H, 9·5. $C_{10}H_{15}NO$ requires: C, 72·69; H, 9·15%). In the IR spectrum (CCl_4) a band at 1635 cm^{-1} (C=C—C=N) was present; UV: 274 (12,000) nm, NMR (CCl_4): δ 3·64 singlet (OMe), 5·23 singlet (=CH) ppm.

1-*Methyl*-1,2,3,4,4a,5,6,7-*octahydro-7-oxo-quinoline* **5**. 6 g of enol ether **3** and 200 ml water were shaken for 45 min in a stoppered bulb under N_2. Extraction with $CHCl_3$ and evaporation of the organic solvent afforded a residue, which was chromatographed over 60 g alumina. Elution with a mixture of 100 ml ether and 300 ml EtOAc afforded 3·31 g of solid product, recrystallized from ether–hexane, m.p. 79–80°. (Found: C, 72·5; H, 9·4; N, 8·4; O, 9·8. $C_{10}H_{15}NO$ requires: C, 72·69; H, 9·15; N, 8·48; O, 9·68%); NMR spectrum: δ 2·86 singlet (NMe), 3·33 multiplet (α-CH_2) and 5·06 singlet (=CH) ppm.

1,2,3,4,4a,5,6,7-*octahydro-7-oxo-quinoline* **6**. A mixture of 1·87 g of **7**, 75 ml EtOH and 75 ml 2N HCl was refluxed for 2·5 hr under N_2. After cooling, the soln was basified with KOH, till pH = 9, and extracted with $CHCl_3$. After washing the organic fraction with water and drying over $MgSO_4$, the solvent was evaporated to yield 1·77 g of a semi-solid.

Recrystallization from THF–ether afforded 0·68 g of crystals, m.p. 180–182°. (Found: C, 71·2; H, 8·8; N, 9·3. $C_9H_{13}NO$ requires: C, 71·49; H, 8·67; N, 9·26%; NMR spectrum: δ 1·2–2·5 9-proton multiplet; 3·32 multiplet (α-CH_2); 5·19 singlet (=CH) and 6·79 broad singlet (N—H) ppm.

N-*Methyl-6-aza-estra*-4,8(14)-*diene*-3,17-*dione* **13**. 0·104 g of Li were added to a mixture of 1·675 g or **11**, 1·0 ml EtOH and 160 ml methylamine. After discharge of the blue color, methylamine was evaporated, water added and the soln extracted with $CHCl_3$. After washing the organic fraction with water, drying over $MgSO_4$ and evaporation of the solvent 1·7 g of an oil was obtained, IR absorptions at 1690 cm^{-1} (C=C—OMe) and 1650 (C=C—NMe) cm^{-1}.

The oil was dissolved in 18 ml AcOH and 6 ml 1N HCl and the soln magnetically stirred for 2 min in an oil bath at 135°. After quick cooling in ice, 50 ml water was added and the mixture made alkaline with KOH, till pH = 9. Extraction with $CHCl_3$ in the usual manner, yielded 1·4 g of a brown syrup, which was dissolved in EtOH to remove some hydrolysed starting material by filtration. Evaporation of the EtOH gave 1·3 g of syrupy material, which was extracted several times with boiling ether. After cooling the ether extracts to −20°, 0·314 g of **13** was isolated, m.p. 159–162°. Recrystallization from THF–ether afforded the pure compound, m.p. 160–162°. (Found: C, 75·9; H, 8·2; N, 4·8; O, 11·4. $C_{18}H_{23}NO_2$ requires: C, 75·75; H, 8·12; N, 4·91; O, 11·21%); UV: 301 (32,000) nm. NMR: δ 1·15 singlet, (18-Me) 2·92 singlet (N—Me); 4·05 singlet (7-CH_2), 5·17 singlet (=CH) ppm.

According to its spectral characteristics the remaining brown syrup (0·99 g) was sufficiently pure to use it in the reduction step.

N-*Methyl-6-aza*-17β-*hydroxy-estra*-4,8(14)-*diene*-3-*one* **14**. 0·0315 g of $NaBH_4$ was added at 0° to a soln of 0·148 g of **13** in 25 ml MeOH and the mixture stirred for 1 hr. Two drops of AcOH were added and the solvents evaporated. The residue was taken up in 50 ml $CHCl_3$ and the latter soln washed with sat. $NaHCO_3$ aq and water, and dried over $MgSO_4$. Evaporation of the solvent gave a solid material which was crystallized from THF, yield 0·12 g, m.p. 224–224·5° (sublimation). (Found: C, 75·2; H, 8·8; N, 4·8; O, 11·2. $C_{18}H_{25}NO_2$ requires: C, 75·22; H, 8·77; N, 4·87; O, 11·13%); NMR, δ 0·97 singlet (18-Me), 2·91 singlet (N—Me); 3·90 singlet (7-CH_2), 5·18 singlet (=CH) ppm.

The same procedure was applied to the impure **13** (0·99 g) to yield 0·55 g of **14**, after crystallization from THF.

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