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TOTAL SYNTHESIS OF ANTHRASTEROIDS—III[1]

THE PREPARATION OF SOME 3-PHENYL-2,4-DIAZA-ANTHRAESTRANES

K. WIEDHAUP,[2,3] and H. O. HUISMAN
Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands

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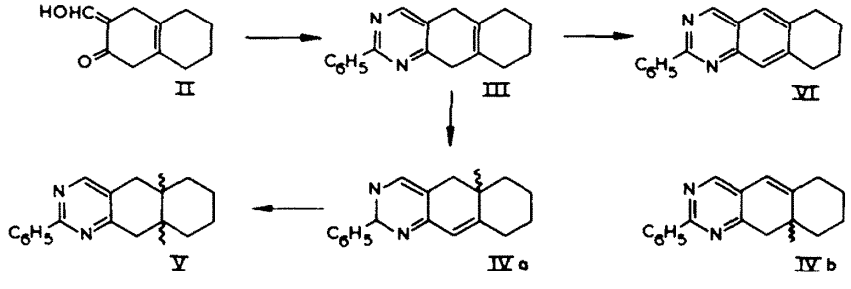
Abstract—Some 6,7-cyclohexano-2-phenylquinazolines have been prepared from 3-hydroxymethylene-$\Delta^{9(10)}$-octalone-2 (II). In a corresponding manner the tricyclic hydroxymethylene ketone I has been converted into a series of 3-phenyl substituted 2,4-diaza-anthraestranes.

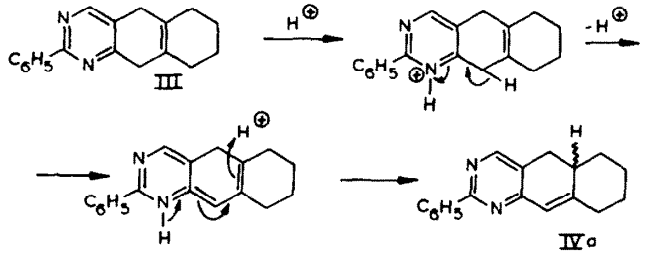
CONTRARY to many recent examples in the steroid field, the preparation of heterocyclic anthrasteroids and aza-anthrasteroids has not yet been reported. As part of our investigations in the total synthesis of anthrasteroids we communicate in this paper the preparation of some 3-phenyl substituted 2,4-diaza-anthrasteroids. As in our synthesis of anthraestrones and anthraequilenines,[1] the tricyclic hydroxymethylene ketone, I,[4] was used as starting material. To determine suitable reaction conditions, preliminary investigations with the bicyclic analogue, II, were carried out. The piperidine catalysed condensation of 3-hydroxymethylene-$\Delta^{9(10)}$-octalone-2 (II) with benzamidine hydrochloride afforded in 78% yield 6,7-cyclohexeno-2-phenyl-5,8-dihydroquinazoline (III) with a UV_{max} at 256 nm (ε = 20,000), characteristic of a 2-phenyl substituted pyrimidine system.[5] Treatment of this dihydroquinazoline,



III, with alcoholic hydrogen chloride gave a single isomeric compound in 90% yield. While the UV (Experimental) and NMR spectra (one proton singlet at δ 6·42) clearly established the conjugated position of the double bond in this system, no unambiguous proof has yet been obtained allowing us to distinguish between the two alternative structures, IVa and IVb. However the NMR results* and the observed selective course of the isomerization reaction suggest IVa to be the more likely product. Its formation can be explained satisfactorily by assuming that the direction of the iso-

* The C-4 proton in the isomerization product was found as a singlet at δ 8·40, while the singlet absorption of the corresponding proton in III was observed at δ 8·45. These values make structure IVb somewhat less probable, since it may be anticipated that the 5(6)-double bond will cause a noticable downfield shift of the heterocyclic proton in IVb as compared with III.[6]

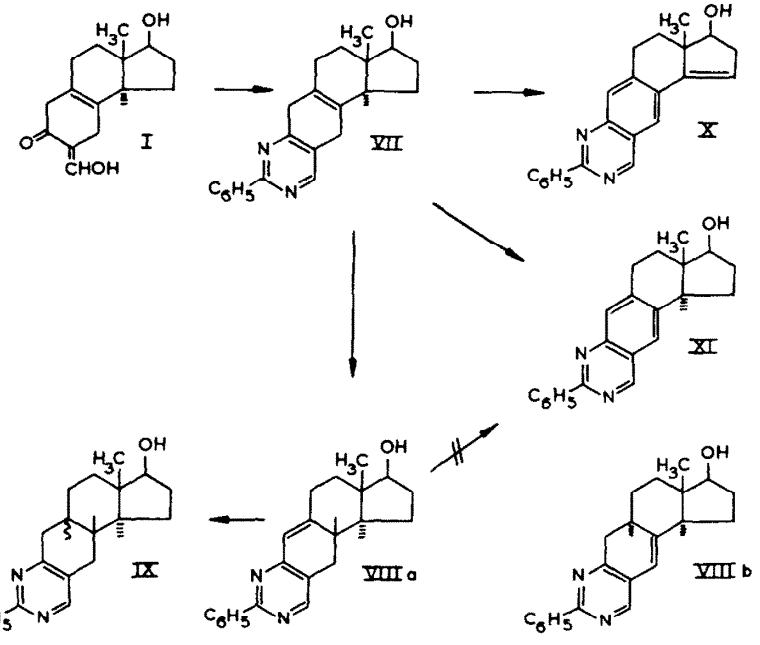
merization is controlled by the electron-attracting property of the nitrogen atom in the 1-position of the pyrimidine ring as shown below:*



Catalytic reduction of the double bond in compound IV gave a mixture of products from which one stereoisomeric form of V was isolated in 68% yield by fractional crystallization.

The dihydroquinazoline III was smoothly dehydrogenated with one equivalent of chloranil to yield the corresponding aromatic system VI, which showed spectral properties (Experimental) in accord with the indicated structure.

In agreement with these model experiments, condensation of the tricyclic hydroxymethylene ketone, I, with benzamidine hydrochloride yielded the 3-phenyl-2,4-diaza-anthraestrane derivative VII of which the spectral characteristics were fully comparable to those of III. When treated with alcoholic hydrogen chloride a single



isomer was obtained in nearly quantitative yield. The NMR spectrum of this substance exhibited a sharp singlet at δ 6·60 for the vinylic proton. The UV spectrum was conformable to that of the tricyclic analogue IV. For reasons outlined earlier this

* A similar tautomerism of the heterocyclic ring has been observed in the aldol condensation at the α-Me group of monocyclic substances as 2-methylpyridine and 4-methylpyrimidine.[7]

isomerization product was provisionally formulated as VIIIa.* Additional support for this assignment may be derived from the observed fast and complete catalytic reduction of the unsaturated bond in this system at room temperature and atmospheric pressure, leading to a crystalline mixture of the two stereoisomeric diaza-anthraestranes IX.† It has been shown[8] that Δ^7-steroids in which rings B, C and D are identical stereochemically to those of VIIIb cannot be reduced catalytically. On the other hand no significant steric hindrance is to be expected in the reduction of a system with structure VIIIa.‡ An 8β-position for the hydrogen atom in VIIIa and thus an *anti-trans* configuration for the system may be anticipated from thermodynamic considerations[9] as well as from the results of related isomerization reactions of intermediates in the synthesis of 19-nortestosterones.[10]

Similar to the observations in the anthrasteroid series,[1] treatment of VII with one equivalent dichlorodicyanobenzoquinone (DDQ) resulted in a mixture of the quinazoline derivatives X and XI. The former system was isolated as the principal reaction product when the dehydrogenation of VII was carried out with two equivalents DDQ, and its structure was evidenced by its spectral properties. The presence of a double bond conjugated with the 2-phenylquinazoline system in X followed from the UV spectrum (see Experimental) and its 14(15)-location was established by NMR. Only *one* vinyl proton signal was observed in the latter spectrum, appearing as a triplet at δ 6·27, thus precluding the alternative 11(12)-position for this unsaturated bond.[1]

The desired diaza-anthraequilenine XI was obtained in pure form by fractional crystallization of the reaction mixture that resulted from treatment of VII with one equivalent DDQ. Its spectral characteristics established unequivocally the indicated structure. The presence of a 2-phenylquinazoline system in XI was confirmed by its UV spectrum, fully comparable to that of the model compound VI. The NMR

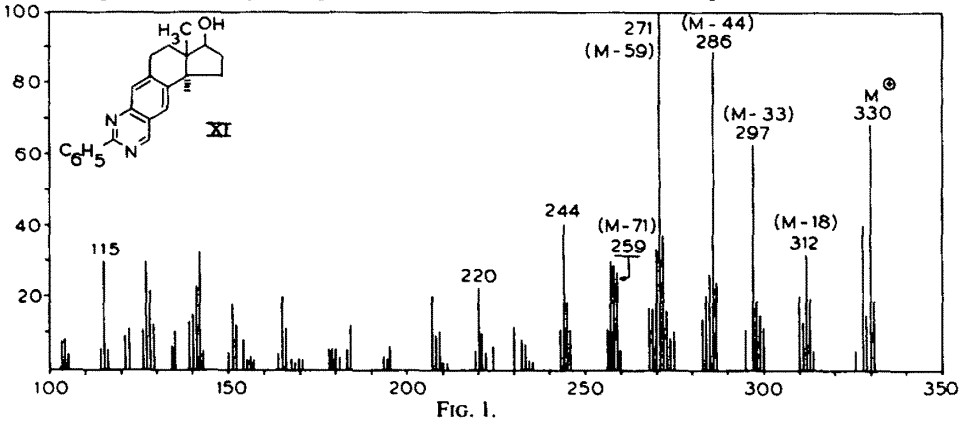


FIG. 1.

* The NMR absorption of the heterocyclic proton in VII was found at δ 8·63; in the conjugated isomer at δ 8·62 (cf. footnote on p. 790).

† While the compositional analysis was in accord with the indicated structure, the presence of two isomers in the reduction product was concluded from its NMR spectrum which exhibited C_{18}-Me absorptions at δ 0·82 and δ 0·85 in nearly equal intensities.

‡ Furthermore, dehydrogenation of the conjugated system to XI with DDQ proved to be impossible even when forcing conditions were applied and lead to an almost quantitative recovery of starting material. This behaviour, most likely resulting from steric factors may be expected for VIIIa but seems less readily explicable for the alternative structure VIIIb.

signal for the C_{18}-Me group appeared at δ 0·62, compatible with the expected *trans*-C/D ring juncture of the substance.[1]

Additional evidence for the structure was provided by its Mass spectrum (Fig. 1) which showed significant similarities to the fragmentation pattern of the 17β-alcohols of anthraequilenine and equilenine.[1]

EXPERIMENTAL

M.ps are uncorrected. UV, IR, NMR and mass spectral measurements were conducted as described in part II.[1] NMR spectra were determined with $CDCl_3$ as the solvent and TMS as the internal reference.

6,7-*Cyclohexeno*-2-*phenyl*-5,8-*dihydroquinazoline* (III). A mixture of 3·90 g (0·022 mole) of II,[4] 4·40 g (0·025 mole) benzamidine hydrochloride hydrate and 1·90 g (0·022 mole) piperidine in 150 ml EtOH was refluxed for 75 hr. After cooling, the mixture was diluted with 5% KOH aq. The crystalline ppt was collected and washed with acetone (0°) to give 4·50 g (78%) of III, m.p. after recrystallization from AcOEt 120–122°. (Found: C, 82·30; H, 6·93; N, 10·78; $C_{18}H_{18}N_2$ requires: C, 82·40; H, 6·92; N, 10·68%); UV (EtOH): 256 (ε = 20,000) nm; IR (KBr): 1590, 1575, 1550, 1435, 1425, 745 and 690 cm^{-1}. In the NMR spectrum a multiplet was observed at δ 3·22 (4p, 5-H_2 and 8-H_2) and a singlet at δ 8·45 (1p, 4-H).

Treatment of III *with methanolic* HCl. The dihydroquinazoline III (0·50 g) was refluxed with 4 ml conc HCl aq in 40 ml MeOH for 4 hr. After cooling, the soln was poured into water and the resulting mixture was basified with KOH aq to afford 0·45 g (90%) of IV, m.p. 145–147°, after recrystallization from EtOH 147–148°. (Found: C, 82·26; H, 6·94; N, 10·78; $C_{18}H_{18}N_2$ requires: C, 82·40; H, 6·92; N, 10·68%); UV (EtOH): 257 (ε = 35,500) and 306 (ε = 7500) nm; IR (KBr): 1630, 1590, 1575, 1545, 1430, 1395 and 690 cm^{-1}. The NMR spectrum exhibited absorptions at δ 6·42 (s 1p, vinylic H) and δ 8·40 (s 1p, 4-H).

6,7-*Cyclohexano*-2-*phenyl*-5,6,7,8-*tetrahydroquinazoline* (V). Hydrogenation of the aforementioned isomer of III (0·26 g) in 35 ml EtOH over 0·09 g Pd–C (10%) afforded, upon working-up a partially crystalline product which gave 0·18 g (68%) of V after fractional crystallization from AcOEt m.p. 151·5–154°. (Found: C, 81·87; H, 7·62; N, 10·63; $C_{18}H_{20}N_2$ requires: C, 81·78; H, 7·63; N, 10·60%); UV (EtOH): 257 (ε = 19,500) and 278 (sh) nm; IR (KBr) 1585, 1570, 1545, 1423, 740 and 690 cm^{-1}.

6,7-*Cyclohexeno*-2-*phenylquinazoline* (VI). A mixture of 0·524 g (0·002 mole) of III and 0·492 g (0·002 mole) chloranil in 20 ml anhyd xylene was refluxed for 5 hr. After cooling and removal of the formed hydroquinone, the resulting soln was diluted with ether and washed with 10% KOH aq (4 times), water and sat NaCl aq. The residue obtained after drying ($MgSO_4$) and evaporation of the solvent was recrystallized from AcOEt to give 0·400 g (77%) of VI, m.p. 123–126°. Further recrystallization from EtOH raised the m.p. to 126·5–127·5°. (Found: C, 83·14; H, 6·18; N, 10·89; $C_{18}H_{16}N_2$ requires: C, 83·04; H, 6·20; N, 10·76%); UV (EtOH): 267 (ε = 39,000), 330 (ε = 5000) and 343 (sh) nm; IR (KBr): 1625, 1590, 1575, 1550, 1490, 1430, 1380 and 760 and 700 cm^{-1}. The NMR spectrum showed absorptions at δ 1·84 (m 4p, 2'-H_2 and 3'-H_2), δ 2·98 (m 4p, 1'-H_2 and 4'-H_2) and δ 9·27 (s 1p, 4-H).

3-*Phenyl*-2,4-*diaza*-*anthraestra*-1,3,5,8-*tetraene*-17β-ol (VII). A mixture of I[4] (0·620 g; 0·0025 mole), benzamidine hydrochloride hydrate (0·500 g; 0·0028 mole) and piperidine (0·210 g; 0·0025 mole) in 25 ml EtOH was refluxed for 72 hr. Working up in the manner described for III yielded crystalline material which was treated with boiling MeOH to give 0·480 g (58%) of VII, m.p. 189–191°, after recrystallization from EtOH 192–193°. (Found: C, 79·50; 7·34; O, 4·98; N, 8·39; $C_{22}H_{24}ON_2$ requires: C, 79·48; H, 7·28; O, 4·81; N, 8·43%); (EtOH): 258 (ε = 20,700) nm; IR (KBr): 3300, 1588, 1578, 1550, 1420, 1080, 1050, 745 and 693 cm^{-1}. The NMR spectrum exhibited absorptions at δ 0·78 (s 3p, 18-Me), δ 3·36 (s 4p, 7-H_2 and 10-H_2), δ 3·88 (t 1p, 17-H) and δ 8·63 (s 1p, 1-H).

Treatment of VII *with methanolic* HCl. After refluxing a soln of 0·40 g VII and 1·6 ml conc HCl aq in 25 ml MeOH for 2·5 hr and isolation of the reaction product in the manner described for the treatment of III with methanolic HCl, 0·38 g (95%) of the conjugated isomer of VII was obtained; m.p. after recrystallization from EtOH 214–215°. (Found: C, 79·50; H, 7·23; O, 4·84; N, 8·56; $C_{22}H_{24}ON_2$ requires: C, 79·48; H, 7·28; O, 4·81; N, 8·43%); UV (EtOH): 259 (ε = 37,000) and 305 (ε = 8400) nm; IR (KBr): 3400, 1630, 1590, 1570, 1540, 1430, 1390, 1050, 750 and 690 cm^{-1}. The NMR spectrum displayed absorptions at δ 0·87 (s 3p, 18-Me), δ 6·60 (s 1p, vinylic H) and δ 8·62 (s 1p, 1-H).

No dehydrogenation products were obtained when the above-mentioned substance was treated with chloranil or DDQ in refluxing xylene for periods up to 60 hr, and in every case starting material was recovered in almost quantitative yield.

Catalytic reduction of VIII. The aforementioned conjugated isomer of VII (0·20 g) was hydrogenated in EtOH over Pd–C (10%) to yield after work-up 0·20 g crystalline material, m.p. 150–170°, after recrystallization from MeOH 155–175°. (Found: C, 78·69; H, 7·82. N, 8·54; $C_{22}H_{26}ON_2$ requires: C, 79·00; H, 7·84, N, 8·38%); UV (EtOH): 256 (ε = 19,500) nm; IR (KBr): 1590, 1575, 1550, 1430, 1050, 745 and 690 cm^{-1}. The NMR spectrum of the crude reaction product showed C_{18}-Me absorptions as singlets at δ 0·82 and δ 0·85 in equal intensities, indicating the presence of two stereoisomers in a ratio of 1:1, provisionally formulated as 9α-IX and 9β-IZ.

3-*Phenyl*-2,4-*diaza-anthraestra*-1,3,5,7,9-pentaene-17β-*ol* (XI). After refluxing a soln of 0·250 g (0·00075 mole) VII and 0·182 g (0·0008 mole) DDQ in 20 ml anhyd benzene for 10 hr and working up the reaction mixture as outlined for VI, 0·240 g crystalline material was obtained. The NMR spectrum of the crude reaction product indicated the presence of ca. 30% X and 70% XI (δ 0·61 (2, 18-Me of XI) and δ 1·08 (s 18-Me of X)). Fractional crystallization of this mixture from $CHCl_3$ followed by recrystallization from AcOEt afforded XI in pure form, m.p. 190–193°. (Found: C, 80·02; H, 6·57; O, 4·88; N, 8·49; $C_{22}H_{22}ON_2$ requires: C, 79·97; H, 6·71; O, 4·84; N, 8·48%); UV (EtOH): 268 (ε = 40,000) and 327 (ε = 5,500) nm; IR (KBr): 3500, 1625, 1590, 1570, 1550, 1480, 1435, 1070 and 760 cm^{-1}. The NMR spectrum exhibited absorptions at δ 0·62 (s 3p, 18-Me) and δ 9·48 (s 1p, 1-H).

3-*Phenyl*-2,4-*diaza-anthraestra*-1,3,5,7,9,14-*hexaene*-17β-*ol* (X). Dehydrogenation of 0·250 g (0·00075 mole) VII with 0·364 g (0·0016 mole) DDQ as described above yielded 0·220 g crystalline material consisting of ca. 85% X and 15% XI, as estimated from the NMR spectrum. Purification by filtration over florisil (eluens $CHCl_3$–EtOH, 1:1) followed by recrystallization from benzene gave the pure hexaene X, m.p. 199–201·5°. (Found: C, 80·33; H, 6·21; O, 5·01; N, 8·53; $C_{22}H_{20}ON_2$ requires: C, 80·46; H, 6·14, O, 4·87; N, 8·53%); UV (EtOH): 269 (ε = 44,000), 278 (ε = 54,000), 313 (ε = 15,200), 358 (ε = 8400) and 372 (sh) nm; IR (KBr): 3480, 1625, 1585, 1565, 1545, 1430, 1065, 1030 and 695 cm^{-1}. In the NMR spectrum absorptions were observed at δ 1·07 (s 3p, 18-Me) and δ 6·27 (t 1p, vinylic H).

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