Tetrahedron Letters No. 34, pp 3187 - 3190, 1973. Pergamon Press. Printed in Great Britain.

MECHANISTIC STUDIES ON THE TOTAL SYNTHESIS OF HETEROCYCLIC STEROIDS: ATTEMPTS OF SYNTHESIS OF 4,6-DIAZASTEROIDS

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(Received in UK 27 June 1973; accepted for publication 6 July 1973)

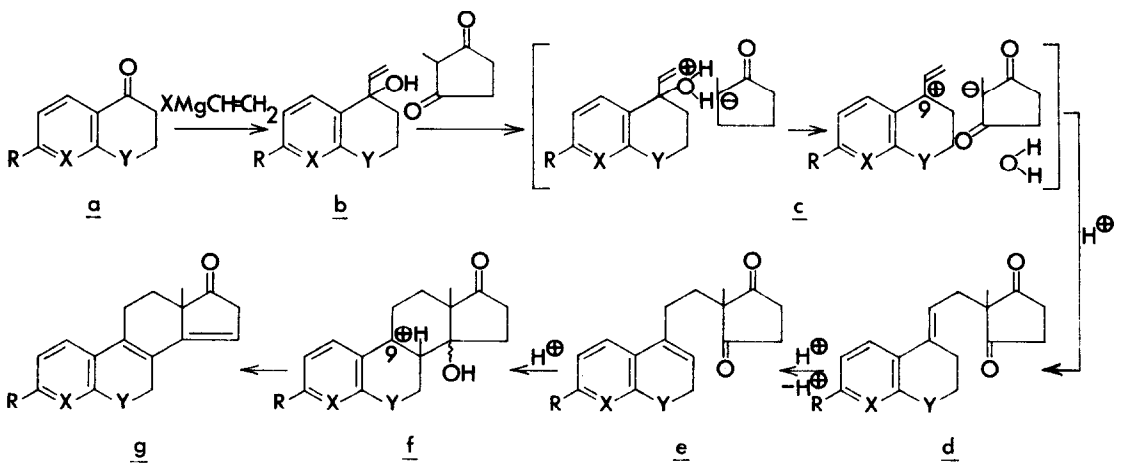
In the application of the so-called Torgov Synthesis[2)] (Scheme 1) to the total synthesis of aromatic azasteroids, the following observations have been made[3)]:

1. The electronic arrangements stabilising a positive charge in position 9 (Scheme 1: steroid nomenclature) will favor the condensation (c) and the cyclisation (f) steps[3a)].

2. The presence of a pyridine ring (e.g., a: X=N, Y=CH_2, R=H) disfavors the formation of a positive charge in carbon 9, both in the condensation (b→d, very slow) and mainly, in the cyclisation (d→g, no reaction at all) steps.

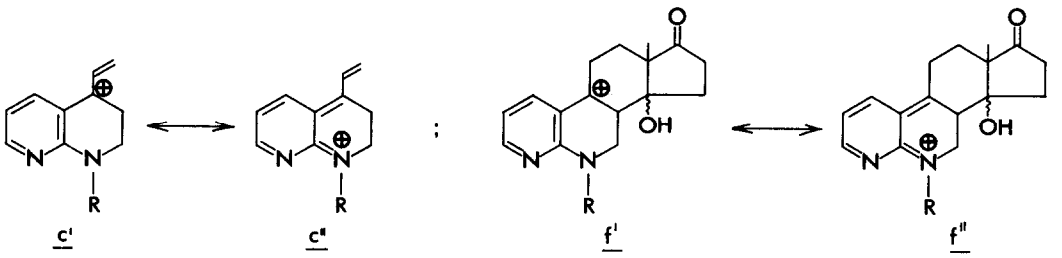
3. The introduction of an electron-donating group in the pyridine ring (e.g., a: X=N, Y=CH_2, R=OC_2H_5) counteracts the previous effect and permits both reactions to proceed satisfactorily.

4. The presence of a nitrogen atom attached to a benzene ring meta-substituted by an electron-donating group (e.g., a: X=CH, Y=N-alkyl, N-alkoyl, N-tosyl or N-acyl, R=OC_2H_5) also favors both reactions. This result cannot be attributed merely to the electron-donating group, since it has been shown that with other heteroatoms in the same position (e.g., a: X=CH, Y=SO_2, R=OC_2H_5), neither the condensation nor the cyclisation take place.



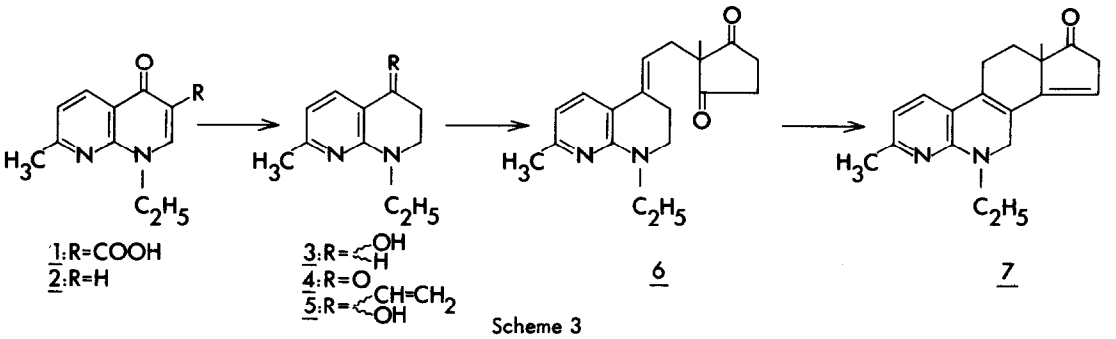
Scheme 1

The purpose of this work has been to elucidate whether an α-N-dialkyl substituted pyridine would behave as an "activated" pyridine allowing the inclusion of both nitrogen atoms in the steroid skeleton (significance of the mesomeric forms c" and f", Scheme 2).



Scheme 2

As a model process, nalidixic acid (1: 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-2-carboxylic acid), was acid decarboxylated to 2[4] (Scheme 3): m.p. 93-4°[5] and all the analytical and spectral data in accord with the assigned structure.



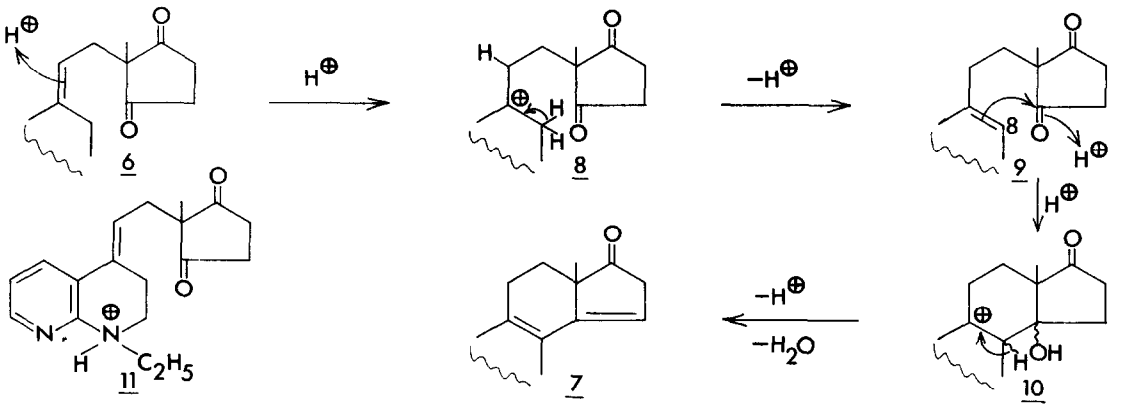
Scheme 3

The saturation of the 2-3 double bond, which is very resistant to catalytic hydrogenation[6], was carried out in very high yield, as follows: first, treatment of 2 with $NaBH_4$ in ethanol at room temperature gave 3 (m.p. 47-9°; $\nu_{max}^{(film)}$ = 3350,1605,1580,1500 cm^{-1}; $\lambda_{max}^{(EtOH)}$ = 256 nm (ε = 17.600), 319 (ε = 7.000); δ ($CDCl_3$)[7] = 1.14/t/J=7(3)N-CH_2-$\underline{CH_3}$, 1.88/m(2)3-H_2, 2.34/s(4)7-CH_3+4-OH (the alcoholic proton signal shifts to higher field when slightly heating the sample), 3.08-3.95/m(4)N-$\underline{CH_2}$-CH_3+2-H_2, 4.60/t/J=4(1)4-H, 6.28/d/J=7.5(1)6-H, 7.5/d/J=7.5(1)5-H ppm; m/e=174(M^+-18; the elemental analysis confirmed $C_{11}H_{16}N_2O$). Compound 3 was the oxidised to 4 (100% yield), by means of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene at room temperature. The product, a viscous liquid, displayed the following absorption bands and signals: $\nu_{max}^{(film)}$ = 1675, 1590,1570,1370 cm^{-1}; $\lambda_{max}^{(EtOH)}$ = 224 nm (ε = 19.000),269(ε = 11.700),383 (ε = 31.000); δ ($CDCl_3$)=1.18/t/J=8(3)N-CH_2-$\underline{CH_3}$, 2.41/s(3)7-CH_3, 2.65/t/J=7(2)3-H_2, 3.51/t/J=7(2)2-H_2, 3.75/c/J=8(2)N-$\underline{CH_2}$-CH_3, 6.44/d/J=8(1)6-H, 7.91/d/J=8(1)5-H ppm; the molecular-ion peak in the mass spectrum and the elemental analysis of the picrate (m.p. 144-5°) confirmed the empirical formula $C_{11}H_{14}N_2O$ for 4.

The reaction of 4 with a molar equivalent of vinyl lithium at -70° under N_2 gave, in almost quantitative yield, the allylic alcohol 5, an oil very unstable in the presence of air. A sample, purified by thin layer chromatography showed the following spectroscopic data: $\nu_{max}^{(film)}$ = 3410, 1595,1575,1500 cm^{-1}; δ ($CDCl_3$)= =1.12/t/J=7(3)N-$CH_2\underline{CH_3}$, 1.6-2.2/m(3)3-H_2+4-OH, 2.30/s(3)7-CH_3, 3.0-3.5/m(2)3-H_2, 3.66/c/J=7(2)N--$\underline{CH_2}$-CH_3, 5.0-6.0/m(3) vinylic protons, 6.19/d/J=8(1)6-H, 7.12/d/J=8(1)5-H ppm. Short reflux of the rest of the material with 2-methyl-1,3-cyclopentanedione and a trace of acetic acid in benzene-alcohol solution under N_2, gave 6, also in practically quantitative yield. Compound 6, of low stability, exhibited the following spectroscopic data: $\nu_{max}^{(film)}$ = 1765,1725,1590,1570 cm^{-1}; δ ($CDCl_3$)=1.13/t/J=7(3)N-CH_2-$\underline{CH_3}$, 1.17/s(3) 18-CH_3, 2.34/s(3)3-CH_3, 2.54/d/J=8(2)12-CH_2, 2.41-3.00/m(4)15-CH_2+16-CH_2, 2.68/t/J=7(2)8-CH_2, 3.27/t/J=7(2)7-CH_2, 3.66/c/J=7(2)N-$\underline{CH_2}$-CH_3, 5.54/t/J=8(1)11-CH, 6.28/d/J=7(1)2-CH, 7.29/d/J=7(1)--CH; m/e=312(M^+). Finally, all attempts to cyclize the secosteroid 6 to 7 failed: various acid catalysis (e.g., HCl, polyphosphoric or acetic acid) with different solvents and temperatures gave as a result a 100% recovery of 6 or its total decomposition.

These results point to an apparently contradictory effect of the nitrogen atom in position 6: it favors the condensation reaction (5→6) but disfavors the cyclisation step (6→7). Both facts are, nevertheless, in accordance with the proposed mechanism[3]:

1. 2-Methyl-1,3-cyclopentanedione is acidic enough to catalyse its condensation with the allylic alcohol (Scheme 1). The reaction medium is weakly acidic, has practically no effect on the associate ion pair c and the stabilising mesomeric form of type c" (Scheme 2) is significant. In fact, the reaction seems to take place more readily than in the case of the monoheteroatomic analogs (e.g., b: X=N, Y=CH_2, R=H)[8].
2. In the cyclisation step, a more detailed mechanism has been proposed[9)3a] (Scheme 4: 6→9→10→7). The double bond isomerisation could proceed through 6→8→9. As the reaction normally takes place in strong acidic medium, a high proportion of the protonated structure 11 should exist, disfavoring the resonance stabilisation of both carbonium ions 8 and 10.



Scheme 4

Since for the condensation step an unsaturation in position 8 seems to be required (9), the use of double bond isomerising catalysts has been essayed but without success. Also, the direct use of the unsaturated derivative 2 was attempted, but the effect of this modification could not be investigated since compound 2 gives 1,4-addition products to the pyridine ring with lithium derivatives[10].

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