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N-BENZOYLOCTAHYDRO-7(1H)-QUINOLONE. EXCLUSIVE ISOMERIZATION OF THE RING JUNCTION TO CIS RATHER THAN TRANS FUSION

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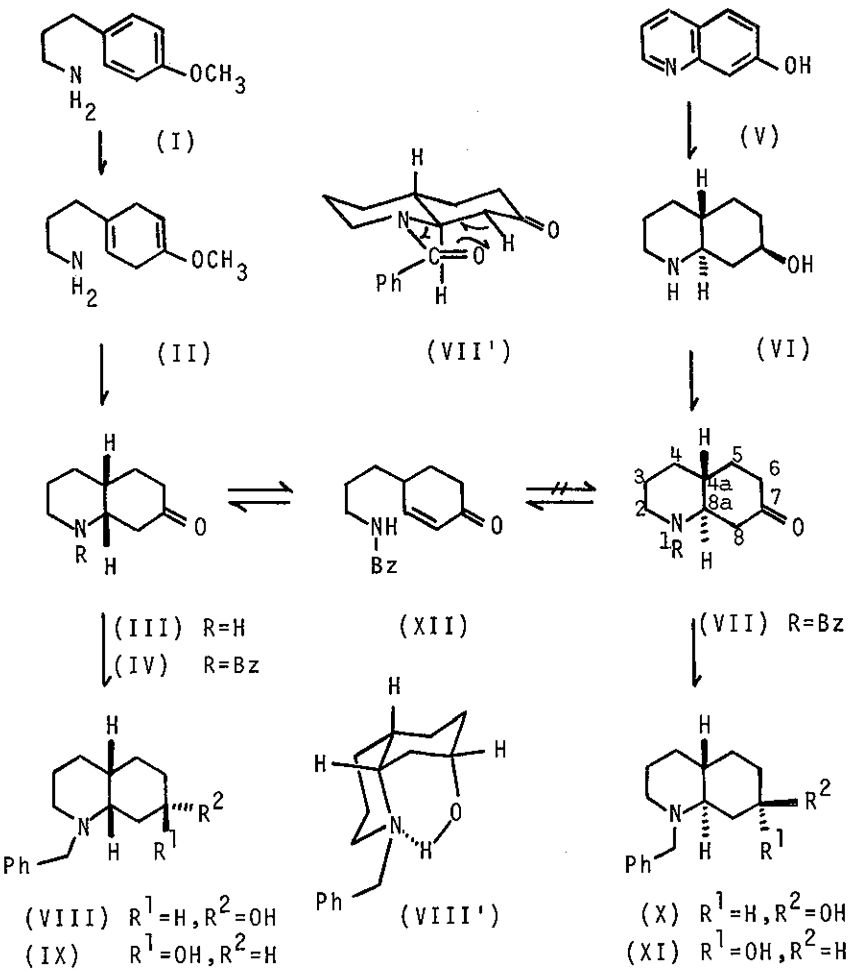
The synthesis and stereochemistry of trans- and cis-octahydro-7(1H)-quinolones are described. There was found a marked stability of cis- rather than trans-configuration of N-benzoyloctahydro-7(1H)-quinolone system.

Octahydro-7(1H)-quinolones are of interest as a key intermediate for the Lycopodium- and Aspidosperma-alkaoid synthesis[1] and their stereochemistry has often been the subject of controversy as in the 4a-ethyl derivative[1b,2]. We synthesized cis- and trans-N-benzoyloctahydro-7(1H)-quinolone and found the former to be unexpectedly stable rather than the latter on isomerization experiments.

Birch reduction of 3-(p-methoxyphenyl)-1-propylamine (I)[3] gave the dihydro compound (II), b.p. 97-103° (2 mmHg), in 77% yield, which on acid hydrolysis afforded cis-octahydro-7(1H)-



quinolone (III), m.p. 68.5-70.5°, IR $\nu_{max}^{CHCl_3}$: 1710 cm^{-1}, in 75% yield. Its benzamide (IV), m.p. 117-118°, shows NMR signal of two deshielded protons, as broad one in 3.6-5.1 ppm region, attributable to those attached equatorially to C_2 and C_{8a}[4].

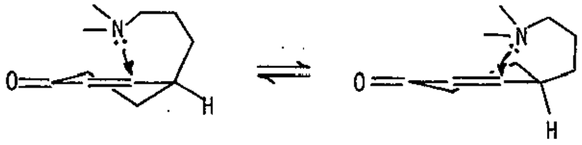
The trans-isomer was synthesized starting with hydrogenation of a quinoline derivative. 7-Hydroxyquinoline (V)[5] was hydrogenated over 5% rhodium on alumina in a similar condition to that for quinoxaline[6] to give the saturated amino-alcohol (VI)[7], m.p. 169-171°, as the main product (45% yield[8]). N-Benzoylation and subsequent Jones oxidation of the amino-alcohol (VI) afforded trans-N-benzoyloctahydro-7(1H)-quinolone (VII), m.p. 106-108°. The NMR spectrum of VII exhibits no aliphatic proton signal at the field lower than 3.85 ppm[4].

Lithium aluminum hydride reduction of IV and VII gave all of four possible N-benzylquinolols; VIII and IX (5:1) from IV, and X and XI (7:1) from VII. And merely one isomer (VIII) exhibits intramolecular hydrogen bonding in IR spectrum (3350 cm^{-1}, 4 mM in CCl_4), concluding the cis-configuration for IV. It is striking that hydrogenation of V over rhodium catalyst gave the trans-isomer (VI) in rather high yield[9].

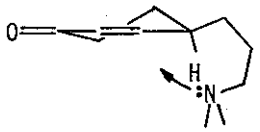
There has been described[7,10] that cis-octahydro-7(1H)-quinolone system should isomerize to trans in acidic or basic media through the retro-Michael process or that the trans-system is preferable in stability to the cis-one, but no experimental proof for this prediction has been reported[11]. Treatment of the cis-isomer (IV) with p-toluenesulfonic acid in boiling benzene for 25 hours afforded no trans-isomer (VII) but the α,β-unsaturated ketone (XII), m.p. 90.5-91.5°, IR $\nu_{max}^{CHCl_3}$: 3400 (NH) and 1665 cm^{-1} (ketone and amide), MS: m/e 257 (M^+), NMR ($CDCl_3$) δ: 5.97 and 6.82 ppm (two olefinic protons), in 23% yield with recovery of the starting material (IV, 50%). Similar treatment of the trans-isomer (VII) gave the cis-isomer

(IV) and the ketone (XII), in 48% and 20% yield, respectively. No such isomerization was detected in basic media. This isomerization feature or the exclusive formation of III from II can be interpreted by assuming a predominant cis-attack (A) in preference to trans-one (B) in the Michael-type addition step due to a favorable steric requirement for an approach of the nitrogen atom to the conjugated system[12].

A marked stability of the cis-configuration of N-benzoyloctahydro-7(1H)-quinolone suggests the importance of the kinetic effects on the configurational stability of this system and that the isomerization feature of the quinolones does not always correspond to a free energy change.



(A)



(B)

References and Footnotes

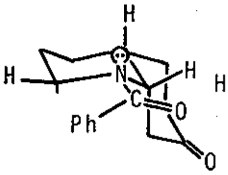
1 (a) Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanaoka, *Tetrahedron Letters*, 1965, 2261; (b) G. Stork and J. E. Dolfini, *J. Amer. Chem. Soc.*, 1963, **85**, 2872; (c) H. Dugas, M. E. Hazenberg, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 1967, 4931.

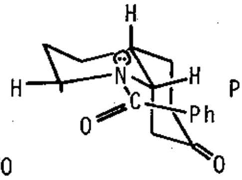
2 G. Stork and his coworker[1b] synthesized 4a-ethyloctahydro-7(1H)-quinolone from 4-(3-aminopropyl)-4-ethyl-2-cyclohexenone ethylene ketal. They assigned its ring fusion as trans, but this assignment was revised as cis [Y. Ban, I. Inoue, M. Akagi, and T. Oishi, *Tetrahedron Letters*, 1969, 2067].

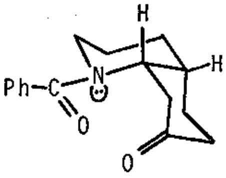
3 A. W. Fort and J. D. Roberts, *J. Amer. Chem. Soc.*, 1956, **78**,

584.

4 On the analogy of cis-decahydroquinoline system bearing N-substituents larger than methyl group [H. Booth and D.V. Griffiths, J. Chem. Soc. Chem. Commun., 1973, 666], the type (i) conformation should be preferred and accordingly permits of two stable rotamers (E and Z) in which the amide carbonyl can exert a considerable deshielding effect to adjacent C_2- and C_{8a}-equatorial protons. In the trans-system, only the E-rotamer (iii) should be stable, because of a steric interference by C_8-methylene, where no significant deshielding effect over adjacent protons operates. An analogous feature can be found in N-benzoyldecahydroquinoline [H. Booth and A. H. Bostoch, J. Chem. Soc. Perkin II, 1972, 615].


(i-E)


(i-Z)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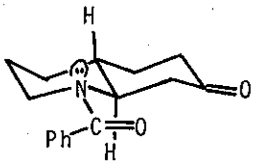
(iii)

5 E.Fujita, T. Saijoh, and N. Takao, Yakugaku Zasshi, 1954, 74, 206; L. Bradford, T.J. Elliott, and F.M. Rowe, J. Chem. Soc., 1947, 437.

6 H.S. Broadbent, E.L. Allred, L. Pendleton, and C.W. Whittle, J. Amer. Chem. Soc., 1960, 82, 189.

7 C.A. Grob and H.J. Wilkens, Helv. Chim. Acta, 1965, 48, 808.

8 The value from one recrystallization of the row product. The remaining recrystallization residue was found to be a mixture of the cis- and trans-quinolols.

9 Further results on the hydrogenation and the related mechanistic consideration will be published in a separate paper.

10 R.V. Stevens, R.K. Mehra, and R.L. Zimmerman, Chem. Commun., 1969, 877.

11 We have recently established the validity of this prediction at least in N-alkyl derivatives [unpublished work].

12 The retro-Michael-type cleavage of VII, where the opening bond (C_{8a}-N_1) is equatorial to the cyclohexanone ring, seems to proceed via a cyclic transition state as depicted in VII'.