5. V. M. Sutyagina, V. P Lopatinskii, and V. D. Filimonov, Vysokomol. Soedin., Ser. A, No. 9, 1968 (1982).
6. V. S. Poplavskii, V. A. Ostrovskii, G. I. Koldobskii, and E. A. Kulikova, Khim. Geterotsikl. Soedin., No. 2, 264 (1982).
7. V. P. Shipanov, Khim. Geterotsikl. Soedin., No. 8, 1130 (1983).
8. M. Charton, J. Org. Chem., 29, 1222 (1964).
9. P. Bouchet, C. Coquelet, and J. Elguero, J. Chem. Soc., Perkin Trans. 2, No. 5, 449 (1974).
10. T. Kauffmann, Angew Chem., 83, 798 (1971).
11. I. Kaczmarek, H. Smagowski, and Z. Grzonka, J. Chem. Soc., Perkin Trans 2, No. 12, 1670 (1979).
12. P. N. Gaponik, O. A. Ivashkevich, and M. M. Degtyarik, Inventor's Certif., No. 1,028,689 (USSR); Byull. Izobret., No. 26, 23 (1983).
13. V. A. Chuiguk, Inventor's Certif., No. 504,772 (USSR); Byull. Izobret., No. 8, 5 (1976).
14. W. G. Finnegan and R. A. Henry, US Pat., 3,004,959; Chem. Abstr., 56, 15510.

STEREOCHEMISTRY OF NITROGENOUS HETEROCYCLES. 61.* SYNTHESIS AND CONFIGURATION OF AN EIGHTH ISOMER OF 2-METHYL-4-HYDROXYDECAHYDROQUINOLINE

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Reduction of 1-benzoyl-2α-methyl-4-oxo-cis-decahydroquinoline with sodium borohydride and sodium in alcohol has given 1-benzoyl-2α-methyl-4β-hydroxy-cis-decahydroquinoline, which exists in the steroidal conformation with diaxial α, α'-substituents in the piperidine ring and with an equatorial hydroxy-group. Debenzoylation of this has given the last of the eight theoretically possible isomers of 2-methyl-4-hydroxydecahydroquinoline, namely 2α-methyl-4β-hydroxy-cis-decahydroquinoline, which exists in the nonsteroidal conformation with an axial hydroxy-group.

By reducing isomers of 2-methyl-4-oxodecahydroquinoline and its derivatives, we have previously obtained seven isomers of 2-methyl-4-hydroxyquinoline [2-6]. Three of the isomers of 2-methyl-4-oxodecahydroquinoline capable of existence (the α-, β-, and γ-isomers) and their N-benzoyl derivatives gave two epimeric alcohols each, and the fourth, δ-isomer (2α-methyl-4-oxo-cis-decahydroquinoline† in the form of its 1-benzoyl derivative (I), on hydrogenation over a nickel catalyst gave a single amidoalcohol (II) in 92% yield [3]. On heating this with benzoyl chloride followed by hydrolysis of the resulting benzoate, a seventh isomer of 2-methyl-4-hydroxyquinoline was obtained which existed in the nonsteroidal conformation (IIIa) with an equatorial hydroxy-group [7]. On the assumption at that time that the conformation of the amidoketone (I) was the same as in the alcohol (IIIa) (i.e., nonsteroidal (Ia)), we employed a method for the preparation of the epimeric alcohol (V) with an axial hydroxy-group which gives preferentially axial alcohols, namely reduction with aluminum isopropoxide (Barton's rule [8]). It was, however found that in this instance the same amidoalcohol (II) was obtained, in even greater (almost quantitative) yields [5].

The present article is devoted to the preparation of the final, eighth isomer of 2-methyl-4-hydroxydecahydroquinoline.

*For communication 60, see [1].
†The trans- (α-) and cis- (β-) dispositions of the substituents are relative to 9-H.

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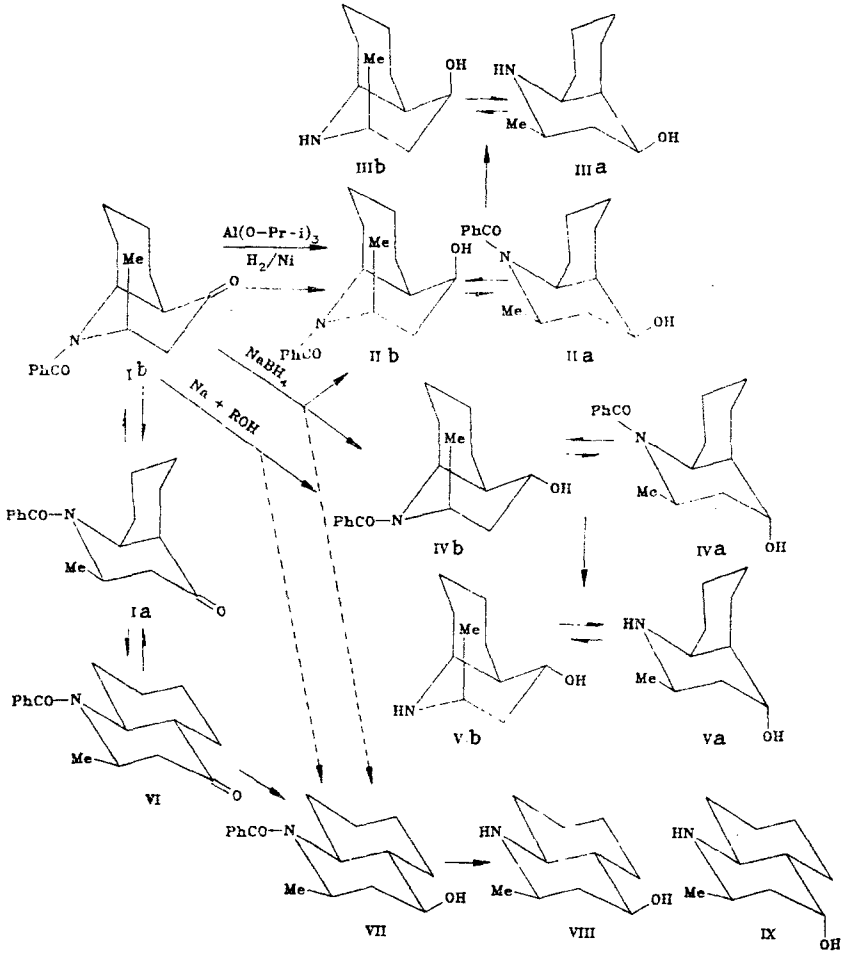
X-ray structural examinations have shown that 1-benzoyl-2α-methyl-4-oxo-cis-decahydroquinoline (I) exists in the steroidal conformation (Ib), with two axial substituents in the α,α'-positions of the piperidine ring [9]. The reason for the greater stability of conformation (Ib) is the tendency of the molecule to free itself from equatorial substituents in the α-positions of the piperidine ring, which interfere with the conjugation of the free electron pair of the nitrogen atom with the π-electrons of the amide carbonyl group. This conjugation is energetically favored to such an extent that it overcomes the repulsive interactions arising in conformation (Ib) in the decahydroquinoline moiety of the molecule. X-ray structural studies have thrown light on the earlier reductions of the amidoketone (I), as follows. Since the ketone (I) exists in conformation (Ib), with the keto-group strongly hindered from the axial side, adsorption on the catalyst and hydrogenation take place from the equatorial side to give the axial alcohol (IIb). Following removal of the benzoyl group, the alcohol (III) adopts the thermodynamically more favored conformation (IIIa) with an equatorial hydroxy group. This reaction takes place with even greater stereospecificity on reduction with aluminum isopropoxide to give nearly quantitative yields of the alcohol (IIb).



It was, however, unclear whether amide conjugation could retain the conformation of the amidoalcohol (II) in the form (IIb), with three 1,3-diaxial $CH_2(CH_3)...OH$ interactions and one 1,3-diaxial $CH_3...CH_2$ interaction. X-ray structural analysis showed [1] that the alcohol (II) in fact exists in conformation (IIb). Hence, the energy of amide conjugation in the alcohol (II) may be taken to be not less than 8 kcal/mole.

It followed from these studies that in order to obtain the eighth isomer, 2α-methyl-4β-hydroxy-cis-decahydroquinoline, with an axial hydroxy group (V), it would be necessary to use methods of reduction leading to the formation of equatorial, rather than axial, alcohols, since following removal of the benzoyl protection and ring inversion, the hydroxy-group would become axial. However, in the case of cyclohexanones it is known [10] that even methods which in unhindered ketones give predominantly equatorial alcohols (reduction with lithium aluminohydride), in the presence of a single β-axial substituent (3,3-dimethylcyclohexanone) give mixtures of approximately equal amounts of the axial and equatorial alcohols, and in the presence of two diaxial substituents (3,3,5,5-tetramethylcyclohexanone), the axial alcohol is obtained almost exclusively.

Since the route to the final isomer of 2-methyl-4-hydroxydecahydroquinoline lies through the only stable form of the δ-isomer, its N-acyl derivative (IIb) in which the axial region of the keto-group is strongly hindered, only one route remained, namely to reduce as far as possible the size of the reducing agent in order to reduce the steric hindrance to its approach from the axial region. On the basis of these considerations, we selected as reductants sodium borohydride and sodium in alcohol.

Reduction of amidoketone (Ib) with sodium borohydride gave a mixture of the isomeric amidoalcohols (II) and (IV). Crystallization of this mixture gave the major proportion of the alcohol (II), the residue, enriched in the alcohol (IV), was separated by column chromatography on silica gel. Although the alcohol (IIb) with an axial hydroxy-group was predominant (82%), it was nonetheless possible to isolate 14% of the equatorial alcohol (IVb).

The mass spectrum confirmed a molecular mass of 273 for the amidoalcohol (IVb). The mass spectrum also contained fragment ions with masses M − 15, M − 17, M − 18, and M − 140, indicating the presence of methyl, hydroxy, and benzoyl groups. The IR spectrum showed strong absorption at 3406 (bonded OH stretching) and 1604 cm^{-1} (amide carbonyl). In the PMR spectrum, the signal for the 4-H proton with a chemical shift of δ 4.08 ppm appeared as a triplet of doublets (J = 10.5; 10.5; 4.5 Hz), indicating that it has the axial orientation, with the hydroxy-group being equatorial.

Preparative chromatographic separation of the reaction products gave, in addition to amidoalcohols IIb and IV6, small amounts (1%) of 1-benzoyl-2α-methyl-4α-hydroxy-trans-decahydroquinoline (VII) with trans-coupling of the rings and an equatorial hydroxy-group, corresponding to the second aminoalcohol (VIII) with mp 144°C. The formation of the trans-amidoalcohol (VII) shows that under basic conditions interconversion of the cis- and trans-amidoketones (I) and (VI) takes place via the enol form, and although the equilibrium is strongly shifted towards the amidoketone (I) (in the isomerization of the trans-ketone (VI) to the cis-ketone (I), it was possible to isolate up to 99% of the amidoketone (I) [11]), and consequently the amount of the amidoketone (VI) is very small, being unhindered it is much more easily reduced by sodium borohydride to give preferentially the equatorial alcohol, resulting in the accumulation of the latter in substantial amounts.

Hydrolysis of the amidoalcohol (IV) to the aminoalcohol gave the eighth, final isomer of 2-methyl-4-hydroxydecahydroquinoline (V) with mp 162-163°C. The IR spectrum of the crystalline alcohol showed absorption for the bonded hydroxy-group (3090 cm^{-1}), and for NH stretching vibrations (3273 cm^{-1}). In the PMR spectrum, the signal for the 4-H proton, chemical shift δ 3.73 ppm, was present as a narrow, unresolved peak of half-width 6.5 Hz, corresponding to an equatorial proton and an axial hydroxy group at $C_{(4)}$, and to the conformation (Va). Confirmation of this conformation was provided by the shape of the 9-H signal (δ 3.24 ppm), this appearing as a narrow, unresolved peak of half-width 7.5 Hz.

In accordance with correlations noted previously [12], according to which 4a-hydroxypiperidines have lower R_f values on alumina than the 4e-isomers, the eighth alcohol (Va) (a-OH) should have a smaller R_f value than its $C_{(4)}$-epimer (IIIa) (e-OH), and a greater R_f than the alcohol (IX), which is epimeric to (V) at $C_{(10)}$. In fact, in system C the R_f of (IIIa) was 0.59, (Va) 0.35, and (IX) 0.24.

On boiling with a dioxane solution of HCl, the amidoalcohol (IV) was debenzoylated much more slowly than the amidoalcohol (II), the amide (II) being debenzoylated to the extent of 90% after 11 h, whereas (IV) was only 10% debenzoylated after 200 h. This difference may be due to the lower internal strain in the decahydroquinoline moiety of the amido-alcohol (IV) as compared with (II).

The reduction of the amidoketone (I) with sodium in alcohol differs fundamentally, a mixture of neutral (amide) and basic (amine) products being obtained. The amide fraction, separated by column chromatography on silica gel, consists principally of the starting amidoketone (I) (84% recovery), together with small amounts of amidoalcohols (IVb) (6.6%) and (VII) (1.4%). Hence, reduction with sodium in alcohol, unlike reduction with sodium borohydride, gives none of the amidoalcohol (IIb) with an axial hydroxy-group, which is the principal product when the reduction is carried out with sodium borohydride. The reason for the reaction taking place in this way is that the anion-radical which is initially formed in the reduction with sodium in alcohol, irrespective of its mode of formation, is capable via the tunnel effect of the unbonded electron of undergoing conversion into the thermodynamically more stable conformation with an equatorial oxygen atom (its axial orientation, as will be seen from the

diagram and x-ray structural studies [1], is highly hindered), which is finally fixed by the addition of a hydrogen atom to $C_{(4)}$. Hence, reduction of the amidoketone (Ib) with sodium in alcohol, as a result of steric hindrance at the axial oxygen, proceeds with total stereoselectivity to give the equatorial alcohol. The mechanism of the formation of the amidoalcohol (VII), which has trans-fused rings, is apparently the same as in the reduction with sodium borohydride (amidoketone (I) ⇄ amidoketone (VI) epimerization, reduction).

The amine fraction of the reduction products (yield around 2.6%) is principally, according to TLC and GC, a mixture of the cis-aminoalcohol (V) and the equatorial trans-aminoalcohol (VIII), in a ratio of approximately 3:2 (the chemistry of the formation of the amines is not entirely clear. They could be formed by hydrolysis of the 1-benzoyl derivatives by traces of moisture). The overall yield of alcohols (IV) and (V), allowing for recovery of the starting ketone, was 52%.

X-ray structural studies of the amidoketone (I) and the amidoalcohol (II) have thus led to an understanding of the stereochemical aspects of the reduction of the amidoketone (I), and to the identification of likely routes for the preparation of the final, eighth possible isomer of 2-methyl-4-hydroxydecahydroquinoline, which have been carried out experimentally.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrometer in KBr disks, and PMR spectra on a BS-487 instrument (80 MHz), internal standard HMDS. TLC and column chromatographic separation of the amides was carried out on basic grade III alumina, eluent diethyl ether (system A), and on Silpearl silica gel, eluent diethyl ether (system B) [the R_f values in systems A and B were: I) 0.81; 0.68; VI) 0.84; 0.73; II) 0.67; 0.64; IV) 0.34; 0.36; VII) 0.47; 0.41; 1-benzoyl-2α-methyl-4β-hydroxy-trans-decahydroquinoline (mp 134°C) 0.17; 0.32]. TLC of amines was carried out on basic grade III alumina, eluent a 20:1 mixture of dioxane and water (system C) [R_f values of 2α-methyl-4-oxo-trans-decahydroquinoline 0.98, (III) 0.59, (V) 0.35, (VIII) 0.43, (IX 0.24]. GC analyses were carried out on a Khrom-41 chromatograph with a flame ionization detector, on a glass column (2.4 m × 3 mm) packed with Chromatone N (0.20-0.25 mm) to which 5% PEG 6000 had been applied, temperature 160°C helium flow rate 40 ml/min.

1-Benzoyl-2α-methyl-4-oxo-cis-decahydroquinoline (mp 116-117°C), and the other compounds used as samples, were obtained as described in [2-4].

Reduction of 1-Benzoyl-2α-methyl-4-oxo-cis-decahydroquinoline (I) with Sodium Borohydride To a solution of 10.4 g (0.036 mole) of 1-benzoyl-2α-methyl-4-oxo-cis-decahydroquinoline (I) in 100 ml of ethanol was added 3.2 g of $NaBH_4$ in 25 ml of water. The mixture was boiled for 1 h, and the cooled solution was treated with conc. HCl until slightly acid. To the residue was added 70 ml of water, and the neutral reaction products were extracted repeatedly with chloroform. The extracts were dried over sodium sulfate, the solvent removed, and the residue (10.4 g) recrystallized from benzene to give 7.28 g of 1-benzoyl-2α-methyl-4α-hydroxy-cis-decahydroquinoline, mp 182-183°C. The remaining concentrated mother liquors were applied to a 4 cm diam. column packed with silica gel (400 ml). Elution was carried out with ether, 25 ml fraction being collected. From the first five fractions there was isolated 1.3 g of 1-benzoyl-2α-methyl-4α-hydroxy-cis-decahydroquinoline (II), mp 182-183°C, R_f (system B) 0.64 (the overall yield of (II) was 82%). From fractions 10-12 there was obtained 0.12 g (1%) of 1-benzoyl-2α-methyl-4α-hydroxy-trans-decahydroquinoline (VII), mp 131-132°C (from acetone), R_f (system B) 0.41, giving no depression with an authentic sample, and having an identical IR spectrum [13]. From fractions 14-20 there was obtained, after recrystallization from benzene, 1.49 g (14%) of 1-benzoyl-2α-methyl-4β-hydroxy-cis decahydroquinoline (IV) as colorless crystals, mp 141-142°C, R_f (system B) 0.35. IR spectrum: 3406 (OH), 1604 (C=O), 704, 1498, 1581, 3000, 3024, 3061 cm^{-1} (C_6H_5). PMR spectrum (C_2HCl_5, 80°C), δ: 1.24 (3H, d, J = 7.0 Hz, CH_3); 4.08 (1H, t.d., J = 10.5; 10.5; 4.5 Hz; 4-H); 4.5 ppm (1H, t, 2-H). Found: C 74.5; h 8.4; N 5.2%. M (mass spectrometric) 273. $C_{17}H_{23}NO_2$. Calculated: C 74.7; H 8.4; N 5.1%; M 273.

2α-Methyl-4α-hydroxy-cis-decahydroquinoline Hydrochloride (III). A solution of 10.5 g (0.038 mole) of (II) in 150 ml of dioxane saturated with dry HCl, was boiled for 11 h. The solid which separated was filtered off. Yield 7.11 g (90%), mp 274-276°C; R_f (in system C) 0.59. A mixed melting point with an authentic sample [4] gave no depression.

2α-Methyl-4β-hydroxy-cis-decahydroquinoline (V). A solution of 1.0 g (0.004 mole) of (IV) in 50 ml of dioxane saturated with dry HCl was boiled for 200 h. The solid which separated was filtered off, dissolved in water, acidified, washed with chloroform, the aqueous layer saturate

with potassium carbonate, and again extracted with chloroform. The extracts were dried over sodium sulfate, the solvent removed, and the residue recrystallized from acetone to give 60 mg (9.7%) of colorless crystals, mp 162-163°C, R_f (in system C) 0.35. IR spectrum: 3088 (OH), 1583, 2273 cm^{-1} (N–H). PMR spectrum ($CDCl_3$): δ 1.05 (3H, d, J = 6.2 Hz, 2-CH_3); 3.08 (1H, m, 2-H); 3.24 (1H, halfwidth 7.5 Hz, 9-H); 3.73 ppm (1H, halfwidth 6.5 Hz, 4-H). Found: C 71.0; H 11.3; N 8.0%. $C_{10}H_{19}NO$. Calculated: C 71.0; H 11.2; N 8.2%. There was recovered 0.90 g of the starting amidoalcohol (IV).

Reduction of 1-Benzoyl-2α-methyl-4-oxo-cis-decahydroquinoline (I) with Sodium in Methanol. To a solution of 0.5 g (0.002 mole) of the amido-ketone (I) in 120 ml of methanol was added with stirring over 1.5 h at 20°C 2 g (0.086 mole) of sodium. The mixture was acidified with conc. HCl, and the NaCl which separated was filtered off and washed with alcohol. The solvent was removed, the residue dissolved in water, and the neutral products extracted with chloroform. After drying over sodium sulfate and removal of the chloroform, there was obtained 484 mg (95%) of a colorless crystalline solid. This was dissolved in a small amount of chloroform, and applied to a column of diameter 2 cm containing 100 ml of silica gel. Elution was carried out with ether, and 10 ml fractions collected. From fractions 3-5 there was obtained 424 mg (84%) of unreacted amidoketone (I), R_f (system B) 0.68; from fraction 7–7 mg (1.4%) of the amidoalcohol (VII), R_f 0.41; and from fraction 8 – 33 mg (6.6%) of the amidoalcohol (IV), R_f 0.35. Mixed melting points of these products with authentic samples gave no depression. The aqueous solution following removal of the amides was saturated with potassium carbonate, and the bases extracted with chloroform. After drying, the solvent was removed from the extract to give 8 mg (2.6%) of colorless crystals, which according to TLC (system C) was a mixture of 2α-methyl-4α-hydroxy-transdecahydroquinoline (VIII) (R_f 0.43) and 2α-methyl-4β-hydroxy-cis-deca-hydroquinoline (V) (R_f 0.35). These compounds were also identified by GC, their proportions being 3:2. The overall yield of the amidoalcohol (IV) taking into account recovered amidoketone (I) was 52%.

LITERATURE CITED

1. A. A. Espenbetov, Yu. T. Struchkov, and G. S. Litvinenko, Izv. Akad. Nauk Kaz. SSR, Ser. Khim., No. 2, 70 (1985).
2. D. V. Sokolov, G. S. Litvinenko, and K. I. Khludneva, Zh. Obshch. Khim., 29, 1112 (1959).
3. D. V. Sokolov, G. S. Litvinenko, and K. I. Khludneva, Zh. Obshch. Khim., 29, 3204 (1959).
4. D. V. Sokolov, G. S. Litvinenko, and K. I. Khludneva, Zh. Obshch. Khim., 29, 3556 (1959).
5. D. V. Sokolov, G. S. Litvinenko, and V. I. Artyukhin, Izv. Akad. Nauk Kaz. SSR, Ser. Khim., No. 1, 75 (1962).
6. D. V. Sokolov, G. S. Litvinenko, and M. N. Akimova, Izv. Akad. Nauk Kaz. SSR, Ser. Khim., No. 1, 59 (1962).
7. D. V. Sokolov, G. S. Litvinenko, V. I. Artyukhin, and A. A. Andrusenko, Izv. Akad. Nauk Kaz. SSR, Ser. Khim., No. 4, 73 (1965).
8. D. Barton, in: The Stereochemistry of Cyclohexanes [Russian translation], IL, Moscow (1958), p. 51.
9. G. S. Litvinenko, A. A. Espenbetov, and Yu. T. Struchkov, Izv. Akad. Nauk Kaz. SSR., Ser. Khim., No. 5, 64 (1982).
10. D. C. Wigfield, Tetrahedron, 35, 449 (1979).
11. D. V. Sokolov, V. V. Sosnova, and G. S. Litvinenko, Izv. Akad. Nauk Kaz. SSR, Ser. Khim., No. 3, 63 (1967).
12. G. S. Litvinenko, D. V. Sokolov, and V. V. Sosnova, Izv. Akad. Nauk Kaz. SSR, Ser. Khim., No. 6, 38 (1974).
13. O. V. Agashkin, V. I. Artyukhin, G. S. Litvinenko, T. T. Omarov, D. V. Sokolov, K. I. Khludneva, and S. S. Chastnikova, Atlas of Infrared Spectra of Spatial Isomers of Decahydroquinolines [in Russian], Nauka, Alma-Ata (1969).