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HYDROGENATION OF 3(2H)-ISOQUINOLINONES AND THE STEREOCHEMISTRY OF THE PRODUCTS

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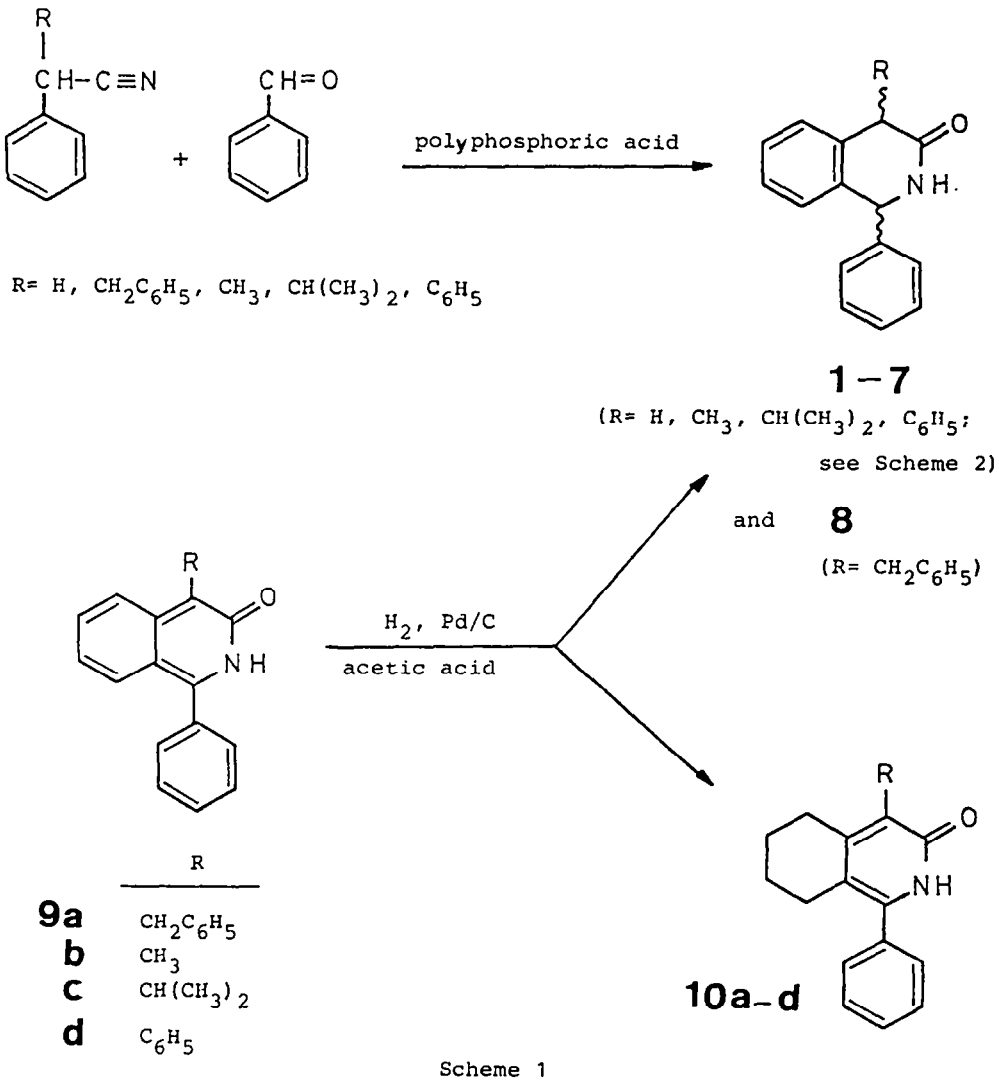
Abstract - A new route of preparing 1,4-dihydro-3(2H)--isoquinolinones and 5,6,7,8-tetrahydroisoquinolinones was developed by the hydrogenation of 3(2H)-isoquinolinones. The 1,4-dihydro compounds 1-8 were also prepared by synthesis, when the cis-trans ratio significantly differed from that of the products obtained by hydrogenation. Relative configurations and site of conformational equilibria were established by n.O.e. difference n.m.r. spectroscopy. Compounds 2,4,5 and 6 had practically one main conformation, whereas 1,3 and 7 occurred as two boat conformers in equilibrium. Complete ^{1}H and ^{13}C signal assignments were achieved by different 2D homo- and heteronuclear correlation measurements.

In the course of developing syntheses of 1-aryl-1,4-dihydro-3(2H)-isoquinolinones by the reaction of arylacetonitriles with aromatic aldehydes, involving cyclization, we reported the preparation of the compound unsubstituted at position 4 (1)[1] and of the 4-benzyl-,[2-4] 4-methyl- and 4-isopropyl[5] derivatives. Of these products, only the stereochemistry of the 4-benzyl-1-phenyl-1,4-dihydro--3(2H)-isoquinolinone was studied.[3,4] The synthesis of 1,4-diphenyl-1,4-dihydro--3(2H)-isoquinolinone is described in a patent,[6] in which the cyclization method is essentially the same as that of Deák and coworkers, but the separation of the stereoisomers 6 and 7 is not mentioned.

Earlier we have also described[7] that catalytic hydrogenation of 4-benzyl-1--phenyl-3(2H)-isoquinolinone, (9a), prepared by us, gave the 5,6,7,8-tetrahydro derivative 10a, saturated in the aromatic ring, as the main product; trans-4--benzyl-1-phenyl-1,4-dihydro-3(2H)-isoquinolinone (8) was formed in a smaller amount. N.m.r. study of the latter compound showed that the C-4 benzyl group was in quasiequatorial and the C-1 phenyl group in quasiaxial position[4].

Since 5,6,7,8-tetrahydroisoquinolinones had not been prepared earlier in this way, but only via the multistep reactions of cyclohexane derivatives, we decided to study the hydrogenation of other 1,4-disubstituted 3(2H)-isoquinolinones. The relative configurations and conformations of the 1,4-disubstituted 1,4-dihydro-

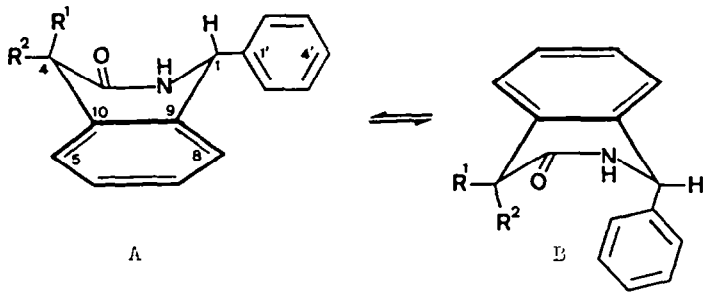


Scheme 1

-3(2H)-isoquinolinones (2-7), formed along with the 5,6,7,8-tetrahydro derivatives, were also determined.

RESULTS AND DISCUSSION

The hydrogenation of 1-phenyl-4-methyl-3(2H)-isoquinolinone (9b) and 1,4--diphenyl-3(2H)-isoquinolinone (9d)[8] in acetic acid, in the presence of Pd/C catalyst, gave the 5,6,7,8-tetrahydro derivatives 10b and 10d, respectively, as the main products in good yields. Besides 10b, a 1,4-dihydro compound (3) was also isolated, which was not identical with the isomer 2, prepared earlier by the cyclization route.[5] In addition to 1,4-diphenyl-5,6,7,8 tetrahydro-3(2H)--isoquinolinone (10d), a mixture of the isomers 6 and 7 was isolated. In contrast with the literature,[6] the same mixture was formed in the synthesis from diphenylacetonitrile and benzaldehyde. The isomers 6 and 7 were separated by means of column chromatography and h.p.l.c. Pure 1-phenyl-4-isopropyl-3(2H)--isoquinolinone (9c) was prepared by a modification of the procedure described



A B

	R^1	R^2
1	H	H
2	CH_3	H
3	H	CH_3
4	$CH(CH_3)_2$	H
5	H	$CH(CH_3)_2$
6	C_6H_5	H
7	H	C_6H_5

Scheme 2

earlier.[9] The hydrogenation of this compound gave the products in reversed ratio; beside less 10c, mainly the 1,4-dihydro isomer (5) was obtained. The analogous compound 4, synthesized by the cyclization method as a crystalline product, was again different from isomer 5.

Both in the hydrogenation and cyclization methods the 1,4-disubstituted 1,4-dihydro-3(2H)-isoquinolinones may be formed as cis-trans isomers. Their identification is rendered difficult since their rapid ring inversion, resulting in an equilibrium of the boat conformers (A⇄B), must be taken into account (Scheme 2). It means that in the cis isomers the substituents are in the 1eq, 4eq or 1ax, 4ax positions and in the trans isomers they are in the 1eq, 4ax or 1ax, 4eq steric arrangement.

Care must be exercised in deciding the preferred steric position of the C-1 and C-4 substituents, as the energies of the two conformers are expected to be very close to each other, because in the equatorial position there appears an unfavourable steric interaction (1,3-allylic strain)[10] between the substituent and the fused aromatic ring. The result is, e.g., that the aryl substituent is quasiequatorial in the C-1 position, and quasiaxial at C-4.[11-13] As in the series Ph, Me and $CHMe_2$, it is the phenyl group which has the least space requirement, for the Me and $CHMe_2$ groups the quasiaxial steric position appears more favourable.

The conditions are modified slightly further in the case of the 1,4-dihydro-3(2H)-isoquinolinones where, owing to the boat conformation and to the presence of the coplanar amide group, the 1,3γ-gauche steric interaction, destabilizing the axial position of the substituents, is further reduced. For the 1-phenyl-4-benzyl-1,4-dihydro-3(2H)-isoquinolinone isomers, studied earlier, we found that the 4-benzyl group was quasiequatorial in both isomers, and the difference between the isomers was due to the different steric positions of the 1-phenyl group; accordingly, the chemical shift of the quasiequatorial 1-H_{eq} is 5.64 p.p.m. in the trans isomer, whereas the shielding of the quasiaxial 1-H_{ax} in the cis isomer is considerably higher, 4.48 p.p.m.[4] In this latter isomer the

steric proximity between the 1-H_{ax} and 4-H_{ax} was also proved by n.O.e. measurements.[4] The characteristic ^1H n.m.r. shifts of compounds 1-7 are summarized in Table 1.

Table 1. ^1H N.m.r. chemical shifts and characteristic coupling constants (Hz) of compounds 1-7 in $CDCl_3$

	1	2	3	4	5	6	7
1-H	5.62	5.63	5.60	5.65	5.66	5.60	5.75
R^1	3.64	1.53	3.55	2.23	3.17[b]	7.20	4.87
				1.07		7.28	
				0.96		7.25	
R^2	3.70	3.56	1.50	3.35[a]	1.61	4.92	7.20
					1.00		7.27
					0.82		7.20
5-H	7.17	7.21	7.20	7.12	7.18	7.13	6.96
6-H	7.23	7.23	7.30	7.20	c	7.25	7.26
7-H	7.16	7.13	7.13	7.06	c	7.16	7.20
8-H	6.94	6.83	6.93	6.56	7.26	6.77	7.04
2'6'-H	7.25	7.25	7.24	7.26	7.30	7.29	7.27
3'5'-H	7.34	7.33	7.26	7.35	c	7.37	7.30
4'-H	7.29	7.3	7.3	7.3	c	7.35	7.28
$^5J(1,4)$	1.9	0	1.5	0	0	0	2.2
	0.5						

[a] $^4J(4,CH)$ = 6.4 Hz; [b] $^4J(4,CH)$ = 8.7 Hz;
c: strongly coupled, overlapping signals between 7.23-7.33 p.p.m.

For signal assignments, the 2D proton-proton (COSY-45)[14] and carbon-proton[15] correlation maps were used. For identifying some of the heavily overlapping signals, data of the 1D n.O.e. measurements[16] were put to use. The results show that the value of δ1-H is here practically insensitive to the relative configuration of the C-1 atom, thus the steric position of the 1-phenyl group cannot be concluded from this signal. The substituents can modify the geometry of the heteroring, also the actual boat A⇄boat B equilibrium may shift; even the conformational equilibrium about the C-1–C-1' and C-4–C-1'' bonds can be different, also influencing the value of δ1-H. Earlier, from the chemical shift, δ1-H = 5.62 p.p.m., of the 1-phenyl derivative (1) it was inferred, by comparison with the corresponding 1-phenyl-4-benzyl isomers, that the 1-phenyl group assumes the quasiaxial steric position.[4] In view of our present investigations, this statement requires some correction.

It is known that in 1,4-crylohexadienes and in their fused-ring analogues the long-range homoallylic coupling constants may provide confirmatory evidence for the establishment of the relative configurations of the 1-H and 4-H atoms. Concerning the three possible interactions, the following order was found: $^5J_{ax,ax} > {}^5J_{ax,eq} > {}^5J_{eq,eq}$ with typical values of 2.5, 1.5 and 0.5, respectively, in systems with aromatic bonds.[17,18]

The $^5J_{(H,H)}$ coupling attains maximum, when the C-H bonds to the coupled protons are nearly parallel; thus, owing to the strong dependence on the geometry, the corresponding spectral data are also insuitable for a quantitative evaluation of the conformational relationships.

In compound 1, the value of 1.9 Hz obtained for the cis $^5J(H,H)$ coupling leads

to the conclusion that this compound has not homogeneous conformation, and in the A⇄B equilibrium one must take into account a considerable contribution of conformer A, containing diaxial 1-H and 4-H atoms. This fact and the steric vicinity of these protons were confirmed by 1D proton-proton n.O.e. difference measurements (see Table 3). The presence of the A-type conformer has to be assumed also in compounds 3 and 7, where cis $^5J_{(H,H)}$ values of 1.5 and 2.2 Hz were found. The value of δH-8 is indicative of the steric arrangement of the 1-phenyl group, since the planes of the two aromatic groups are nearly perpendicular, owing to the steric interaction between the quasiequatorial Ph-1 and the fused aromatic ring; this results in an upfield shift of the δH-8 signal. In the cis 1-phenyl--4-benzyl derivative this effect shifted H-8 signal up to 6.4 p.p.m. If the 1-phenyl group is quasiaxial, such an extent of the diamagnetic effect is not expected; however, the conformation about the C-1—C-1' bond, being in the cis compounds greatly dependent on the substituent at C-4, largely contributes to deciding the value of δH-8. At any rate, in the case of quasiaxial 1-phenyl group, the expected exact value of δH-8 cannot be given. The largest deshielding effect for δH-8 was measured for compounds 5 (7.26) and 7 (7.04), indicating that in the A⇄B equilibrium the ratio of conformer B, containing quasiaxial 1-phenyl group, is the greatest in these substances. In general, δH-5 is insensitive to changes in the C-4 substituent (7.13-7.21 p.p.m.); on the other hand, in compound 7 the diamagnetic effect of the quasiequatorial 4-phenyl group causes an upfield of H-5 (δH-5 = 6.96 p.p.m.). The J(4,CH) = 6.4 Hz coupling constant, measured for the 1-phenyl-4-isopropyl derivative 4, indicates that the population of the three staggered conformers due to rotation arround the C-4-CH bond are nearly the same. The coupling constant of 8.4 Hz in isomer 5 allows the conclusion that, owing to the steric vicinity of the 1-phenyl group, the preponderant conformer will be the one which contains the 4-H and CH protons in antiperiplanar arrangement. Cis configuration and the 1,4-diaxial B conformation are confirmed by the strong shielding of the CH signal; the diamagnetic effect of the nearby 1-phenyl group shifts δCH from 2.23 p.p.m. measured in 4, to 1.62 p.p.m.

The 1D n.O.e. difference measurements were found very useful for the determination of the relative configurations and conformational relations in compounds 1-7. The results are listed in Table 2.

Irradiation of the 1-H signal of 1-phenyl-1,4-dihydro-3(2H)-isoquinolinone resulted in increased intensity of the 4-H(R^1) signal.It follows that, in accordance with the observed $^5J(1,4)$ couplings, conformer A, containing quasiequatorial Ph-1 group, also takes part in the conformational equilibrium. Commensurable occurence of conformers A and B should be taken into account also in the cases of the cis 1-phenyl-4-methyl (3) and 1,4-diphenyl (7) derivatives. The steric proximity of 1-H and 4-H in 3 is confirmed by the n.O.e. data observable from both directions (conformer A); at the same time, the spatial vicinity of the Me-4 and H-2',6' ortho protons, i.e. the presence of conformer B, is substantiated by the increase in intensity of the ortho proton signals on irradiation of Me-4.

The n.O.e. difference measurements led to the conclusion that in compounds 2, 4, 5, and 6 the conformational equilibrium A⇄B is strongly shifted to one side. In the trans compounds 2, 4 and 6, the Ph-1 group is in quasiequatorial position (conformer A), while for the Me-4, iPr-4 and Ph-4 groups the quasiaxial arrangement is more favourable. In the cis 1-phenyl-4-isopropyl derivative (5), the conformational equilibrium is controlled by the very high 1,3-allylic strain concomitant with the quasiequatorial position of the bulky Me_2CH group; consequently, this compound is present as the 1,4-diaxial conformer B. No n.O.e. effect between the 1-H and 4-H protons, revealing the presence of conformer A, could be detected.

Table 2. Results of proton - proton 1D n.O.e. experiments measured at 400 MHz

Compound	Proton irradiated	n.O.e. observed (%)
1	1-H	4-H(R^1) 1.5%, 8-H 5%, NH 2%
2	1-H	4-Me 1.5%, 8-H 3%, NH 3%, 2'6'-H 5%
	4-H	5-H 2%
	4-Me	1-H 3%, 4-H 9%, 5-H 2%
	8-H	1-H 4%, 7-H 3.5%, 2'6'-H 1%
3	1-H	4-H 2%, 8-H 5.5%, NH 5%, 2'6'-H 5%
	4-H	1-H 1.5%, 4-Me 5.5%, 5-H 5%
	4-Me	4-H 7%, 5-H 6%, 2'6'-H 2%
	8-H	1-H 6%, 7-H 6%
4	1-H	4-CH 3.5%, 8-H 2%, NH 1%, 2'6'-H 8%
	4-H	CH (of Pr^i) 2.5%, 5-H 5.5%
	CH (of Pr^i)	1-H 3.5%, 4-H 3.5%, 5-H 1%
	5-H	4-H 6%, 4-CH 1%
	8-H	1-H 2.5%, 7-H 6.5%, 2'6'-H 2%
5	1-H	8-H 4%, NH 3.5%, 2'6'-H 4%
	4-H	CH (of Pr^i) 1%, 5-H 2.5%
	CH (of Pr^i)	4-H 3%, 4-Me 5% and 4%, 5-H 1%, 2'6'-H 4%
6	1-H	8-H 2.5%, 2'6'-H 4%, 2''6''-H 1%
	4-H	5-H 4%, 2''6''-H 2%
	8-H	1-H 1%, 7-H 5.5%
7	1-H	4-H 1%, 8-H 4.5%
	4-H	1-H 1.5%, 5-H 4.5%, 2''6''-H 6.5%
	5-H	4-H 4%
	8-H	1-H 3%

[a] measured at 250 MHz

Table 3. ^{13}C Chemical shifts of compounds 1 - 7 ($CDCl_3$)

	1	2	3	4	5	6	7
1	59.68	59.27	58.93	59.76	59.08	59.52	60.05
3	171.46	174.29	174.32	172.86	173.97	171.53	171.25
4	36.19	40.51	39.53	54.08	54.18	52.39	51.07
5	127.64	126.61	126.17	128.66	129.61	128.73	127.62
6	127.39	127.88	127.43	127.11	127.20[a]	128.02	127.20
7	126.57	126.53	126.72	126.48	126.47	127.08	127.00
8	126.52	126.65	126.59	126.48	127.71	126.56	126.73
9	134.48	134.61	133.46	135.89	133.30	135.80	134.48[a]
10	131.13	137.18	136.73	135.27	136.15	134.95	134.27[a]
1'	141.40	140.86	141.77	140.83	142.32	140.48	141.21
2'6'	126.99	127.70	127.13	128.66	126.56	128.67	128.44
3'5'	128.70	128.92	128.48	128.98	128.61	129.03	128.87
4'	127.80	128.29	127.59	128.58	127.50[a]	128.62	128.27
R^1,R^2	-	17.93	19.31	CH 33.70	CH 32.93	1''138.42	1''139.25
				Me 20.40	Me 21.41	2''128.11	2''129.50
				Me 20.33	Me 20.80	3''128.22	3''127.55
						4''127.23	4''127.76

[a] Tentative assignment

The ^{13}C n.m.r. studies on compounds 1-7 further confirmed the suggested structures. The characteristic chemical shifts of these compounds are summarized in Table 3. In addition to considering the known substituent effects, the assigments of the individual signals were based on 2D carbon-proton correlation maps.[15] Assigments of the quaternary carbon atoms were proved by COLOC[19] and INAPT[20] measurements optimized for the 6 Hz long-range proton-carbon couplings; the measured $^2J(C,H)$ and $^3J(C,H)$ connectivities are summarized in Table 4. Identification of the nearby C-9 and C-10 signals was made possible partly by the COLOC spectrum, in wich cross-peak appeared between the 5-H and C-9 and between the 8-H and C-10 atoms, in accordance with the regularity ($J/C,H_{meta} > J/C,H_{ortho}$) observed for aromatic rings; further in the case of hydrogens, attached to the sp^3 hybridized C-1 and C-4, the geminal J(C,H) couplings proved to be of diagnostic value. Comparison of the ^{13}C chemical shifts of compounds 1-7 obviously shows their great similarity. Differences in the α(C-4), β(C-3 and C-10) and γ^v(C-5) positions were caused practically only by the different substitutions of the C-4 atom. The chemical shifts of the C-1 and C-1' atoms were found insensitive to changes both in the relative configuration and conformation.

Table 4. Determination of carbon - proton connectiyity via ^2J and ^3J couplings by COLOC[a] and INAPT[b] methods

	proton	carbon	
		J	J
1[a]	1-H	1's, 9s	3m, 2'6'w
	4-H	3s, 10s	5m, 9m
	5-H	6w	7s, 9m
	7-H	6w	5m, 9m
	8-H		1m, 6s, 10m
	2'6'-H	3'5'w	4's
3[a]	1-H	1's, 9s	3m, 8w, 10m, 2'6'm
	5-H	6w	4w, 7m, 9m
	6-H		8m
	7-H		5m, 9m
	8-H		1m, 6s, 10m
	2'6'-H	1'm	4's
	3'5'-H	1'm	1's
	4-Me	4m	3s, 10m
4[a]	1-H	1's, 9s	10w, 2'6'm
	4-H	3m	
	5-H		7m, 9m
	6-H		8m, 10w
	7-H		5w, 9w
	8-H		1m, 6s, 10m
	2'6'-H	1'w	4's
	Me	4-CHm	4m
	NH	1m, 3w	9w
5[b]	1-H	9,1'	3, 8, 10, 2'6'
	4-H	3, 10, 4-CH	5, 9, Me_2
	4-CH	4, Me_2	3, 10

symbols s: strong, m: medium, and w: weak, denote the intensity of crosspeaks in the COLOC spectra

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 457 spectrometer in KBr pellets. The n.m.r. spectra were obtained on Bruker AM-400 and AC-250 spectrometers at room temperature. Chemical shifts are given on the δ scale. In the 1D measurements 32K data points were used for FID. For homonuclear n.O.e. experiments a delay time of 3s was applied. N.O.e. difference and two-dimensional carbon-proton correlated experiments were run using the Bruker software package. In the 2D experiments 1Kx1K data matrices were transformed.

M.p.'s (^{o}C) were measured with a Büchi-Tottoli apparatus and are uncorrected.

Hydrogenation of 1-phenyl-4-methyl-3(2H)-isoquinolinone (9b)

Compound 9b (3.11 g; 0.0132 mol) was hydrogenated in 99.5% acetic acid (150 ml), in the presence of 10% Engelhardt's Pd/C catalyst (1 g) as described for 9a[3]. The following products were obtained:

10b: 1-Phenyl-4-methyl-5,6,7,8-tetrahydro-3(2H)-isoquinolinone, 2.3 g (72.8%), m.p. 253-255^{o} (from ethanol). (Found: C, 80.41; H, 7.26; N, 5.85. $C_{16}H_{17}NO$ requires: C, 80.30; H, 7.16; N, 5.85%.) I.r. (KBr):ν C=O 1630 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): H_2-5,8: 2.47 t (2) + 2.63 t (2), H_2-6,7: 1.45-1.90 m (4), CH_3: 2.04 s (3), ArH: 7.40 (A_5, s) (5).

3: cis-1-Phenyl-4-methyl-1,4-dihydro-3(2H)-isoquinolinone, 0.55 g (17.6%), m.p. 132-134^{o}. (Found: C, 81.04; H, 6.49; N, 5.94. $C_{16}H_{15}NO$ requires: C, 80.98; H, 6.37; N 5.90%) I.r. (KBr):ν C=O 1660 cm^{-1}. ^{15}N n.m.r.: δ (p.p.m.) -259.5, ($\delta_{CH_3NO_2}$ = 0 p.p.m.).

The trans isomer 2 had been obtained by the cyclization reaction.[5] The yield of the crystalline product was 37.7%, m.p. 191-193^{o} (from benzene). I.r. (KBr): ν C=O 1680 cm^{-1}. The compound gave correct analysis for $C_{16}H_{15}NO$. Mixed m.p. of the products prepared in the two different ways was 120-126^{o}.

Hydrogenation of 1,4-diphenyl-3(2H)-isoquinolinone (9d)

Compound 9d (7.4 g; 0.0249 mol) was hydrogenated in 99.5% acetic acid (290 ml), in the presence of 10% Engelhardt's Pd/C catalyst (2 g), as described previously.[3] The products were:

10d: 1,4-Diphenyl-5,6,7,8-tetrahydro-3(2H)-isoquinolinone, 4.75 g (63.3%), m.p. 223-224^{o} (from ethanol). (Found: C, 83.76; H, 6.49; N, 4.70. $C_{21}H_{19}NO$ requires: C, 83.69; H, 6.35; N, 4.65%.) I.r. (KBr):ν C=O 1625 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): H_2-7,6: 1.45-1.70 m (4), H_2-5,8: 2.30-2.70 m (4), ArH + NH: 7.0-7.5 m (11). ^{13}C n.m.r. ($CDCl_3$): signals of the sp^{3} hybridized carbon atoms with t multiplicity: 22.0, 22.3, 25.7, 28.8; aromatic signals with s multiplicity: 162.0, 150.4, 147.0, 135.9, 134.0, 128.7; signals of the aromatic carbon atoms with d multiplicity: 130.1, 129.0, 128.4, 128.0, 126.9 (in several cases overlapping of the signals can be observed here).

6,7: Mixture of the stereoisomers of 1,4-diphenyl-1,4-dihydro-3(2H)--isoquinolinone, 1.0 g (13.4%), m.p. 141-159^{o}. (Found: C, 84.49; H, 5.85; N 4.61. $C_{21}H_{17}NO$ requires: C, 84.25; H, 5.72; N, 4.68%). I.r. (KBr):νC=O 1665 cm^{-1}.

Synthesis of 1,4-diphenyl-1,4-dihydro-3(2H)-isoquinolinones (6 and 7) by cyclization

Diphenylacetonitrile (38.6 g; 0.2 mol) was added into a mixture of 85% phosphoric acid (100 ml) and phosphorus pentoxide (100 g). The mixture was heated to 80^{o}, and benzaldehyde (18.5 g; 0.08 mol) was added by drops. It was then stirred at 100^{o} for 1 h, and benzaldehyde (18.5 g; 0.08 mol) was added again.

After stirring for another hour at 100°, the reaction mixture was poured into water (2000 ml) and made alkaline with conc. ammonium hydroxide (400 ml). The precipitated material was filtered off, washed with water and dried to give a mixture of the stereoisomers (33.5 g; 69.8%), m.p. 144-164° (from ethanol). (Found: C, 84.22; H, 5.77; N, 4.66. $C_{21}H_{17}NO$ requires: C, 84.25; H, 5.72; N,4.68.) I.r. (KBr): ν C=O 1665 cm^{-1}.

The trans isomer 6 was isolated as a pure substance by chromatography in $CHCl_3$ on an Al_2O_3 column to obtain 8.73 g (36.4%) of the product, m.p. 197-198°. (Found: C, 84.38; H, 5.74; N, 4.81. $C_{21}H_{17}NO$ requires: C, 84.25 ; H, 5.72; N, 4.68%.) I.r. (KBr):ν C=O 1655 cm^{-1}.

The cis isomer 7 (m.p. 155°) was isolated from the mixture by h.p.l.c.; the conditions were: eluents, n-hexane (40%), n-hexane (w.sat.) (40%), dichloromethane (w.sat.) (14%), acetonitrile (6%), 25% ammonium hydroxide 0.02 ml/100 ml of eluent; column: LiChrosorb 7 Si-100; BST, No. 383; detector: Labor MIM u.v. detector, Type OE-308/1; parameters of measurement: flow-rate 1 ml/min, rate of paper movement 5 mm/min, wavelength 254 mm, attenuation 0.2, voltage 1V; pump: Milton-Roy; retention times: 12 h 54 min for 6 (trans) and 16 h 36 min for 7 (cis).

1-Phenyl-4-isopropyl-3(2H)-isoquinolinone (9c)

The synthetically prepared mixture[5] of 1-phenyl-4-isopropyl-1,4-dihydro-3(2H)--isoquinolinones (4, 5) (2.0 g; 0.0076 mol) was dissolved in dry dimethylformamide (40 ml). Under a stream of nitrogen, at 40°, there was added a 50% dispersion of sodium hydride (1.08 g; 0.022 mol) in oil. The mixture was stirred for 2 h at 135-140°. It was then poured into water (400 ml) and acidified with 2 N hydrochloric acid. The orange-yellow precipitate was filtered off, washed with water, dried, suspended in petroleum ether, and refluxed for a few minutes. After filtration and drying 9c (1.2 g; 60%) was obtained, m.p. 184-186° (from ethanol). (Found C, 82.19; H, 6,70; N, 5.51. $C_{18}H_{17}NO$ requires: C, 82.10; H, 6.51; N, 5.32%.) I.r. (KBr): ν C=N 1615 cm^{-1}.

Hydrogenation of 1-phenyl-4-isopropyl-3(2H)-isoquinolinone (9c)

Compound 9c (1.15 g; 0.004 mol) was dissolved in 99.5% acetic and (100 ml), and hydrogenated in the presence of 10% Engelhardt's Pd/C catalyst (0.4 g), as described for 9a.[3] The following products were obtained:

5: cis-1-Phenyl-4-isopropyl-1,4-dihydro-3(2H)-isoquinolinone, 0.1 g (9.4%), m.p. 169-171°. (Found: C, 81.35; H, 7.20; N, 5.40. $C_{18}H_{19}NO$ requires: C, 81.47; H, 7.22; N, 5.28%.) I.r. (KBr): ν C=O 1665 cm^{-1}.

10c: 1-Phenyl-4-isopropyl-5,6,7,8-tetrahydro-3(2H)-isoqunolinone. Owing to difficulties in separation during column chromatography, this compound could be isolated with maximum 78% purity. It was identified by n.m.r. spectroscopy. (Found: C, 80.47; H, 7.84; N, 5.38. $C_{18}H_{21}NO$ requires: C, 80.86; H, 7.92; N, 5.24%.) I.r. (KBr): ν C=O 1630 cm^{-1}. ^1H n.m.r. ($CDCl_3$): H_2-5: 2.72 t (2); H_2-6.7: 1.4-1.9 m (4); H_2-8: 2.43 t (2); Me_2CH: 1.26 d (6), 3.15 m (1); ArH: 7.40 s (5); NH: 7.28 s (1). ^{13}C n.m.r. ($CDCl_3$): C-1: 147.9; C-3: 162.0; C-4: 134.6; C-4a: 132.6; $(CH_2)_4$: 27.3, 22.4; 22.7; 26.4; C-8a: 114.0; Ph-1: 140.2, 128.4, 129.0 and 128.7.

Yields of the products calculated on the basis of n.m.r. measurements: 10c, 33.4%; 5, 51.2%.

Data of the trans isomer 7 prepared by the cyclization reaction[5] are: yield of crystalline product, 29%; m.p. 179-181° (from benzene). I.r. (KBr): ν C=O 1670 cm^{-1}. The analysis of the compound was consistent with the composition $C_{18}H_{19}NO$.

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