CONFIGURATIONS OF STEREOISOMERS OF 1-(3-PHENYLPROP-2-YNYL)-2-METHYLDECAHYDROQUINOL-4-ONE AND THE CORRESPONDING ACETYLENIC ALCOHOLS

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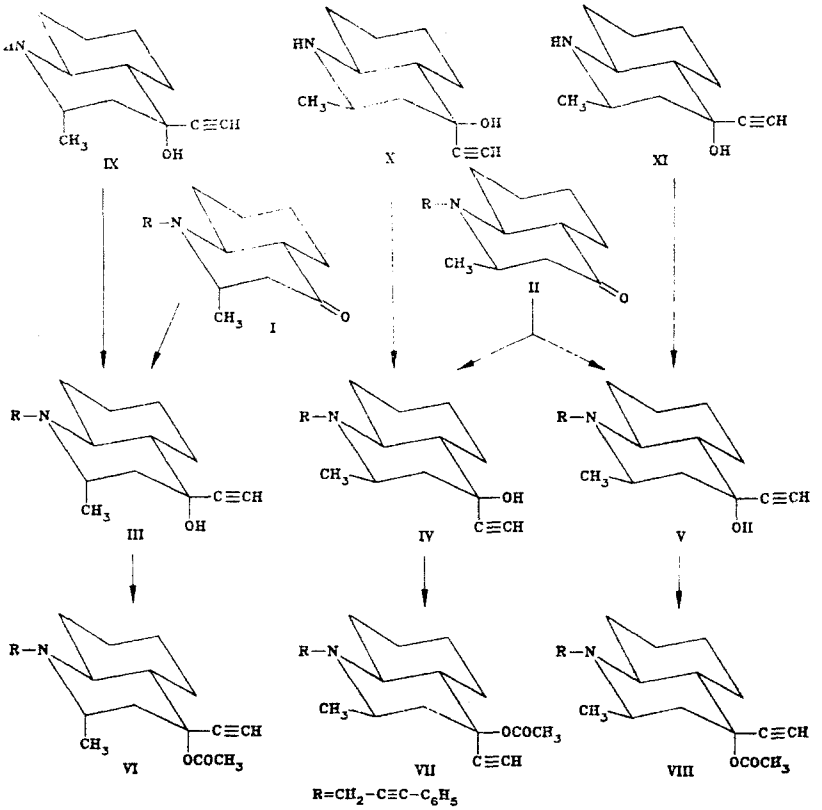
IR and PMR spectroscopy and chemical methods have been used to establish the structures of stereoisomeric 1-(3-phenylprop-2-ynyl)-2-methyldecahydroquinol-4-ones and the corresponding acetylenic alcohols.

We have previously described [1] the synthesis of two isomers of 1-(3-phenylprop-2-ynyl)-2-methyldecahydroquinol-4-ones (I, II), and of the three corresponding acetylenic alcohols (III-V). We have now examined their configurations, and arrived at some conclusions concerning the stereodirectivity of the addition of acetylene to ketones (I) and (II).



In order to establish the mode of coupling of the rings and the orientation of the substituents at $C(_2)$ in (I-VIII), it is sufficient to know the vicinal spin coupling constants for the angular 9-H and 10-H protons and for the 2-H protons with their neighbors.

In the PMR spectrum of the ketone (I), two quartets of protons are seen for $C(_3)$ with $^3J_{HH}$ constants (Table 1) characteristic of the axial 2-H proton. Consequently, the methyl group is axially disposed. The signals for protons 9-H and 10-H fall within the resonance region of the $C(_3)$ protons. Deuteration of ketone (I) under keto-enol tautomeric conditions enabled the chemical shifts and the coupling constants of these protons to be measured.

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TABLE 1. PMR Spectral Parameters of Stereoisomeric 1-(3-phenylprop-2-ynyl)-2-methyldecahydroquinol-4-ones (I, II) and Their Hydrochlorides (in $CDCl_3$)

Compound	δ, ppm								J, Hz						
	2-CH_3	2-H	3-H_a	3-H_e	9-H	10-H	N—CH_2	Ph	2-H—2-CH_3	2-H—3-H_a	2-H—3-H_e	3-H_a—3-H_e	9-H—10-H	9-H—8-H_a	9-H—8-H_e
I	1,11	3,79	2,91	2,13	2,72	2,23	3,74	7,24	6,5	5,5	2,0	13,0	10,0	10,0	2,5
I*	1,37	4,31	3,43	2,35	3,31	2,83	4,14	7,33	6,5	5,7	2,0	13,7	10,0	10,0	2,5
II	1,22	2,91	2,34	2,34	—	—	3,85	7,26	6,0	7,0	7,0	—	—	—	—
II*	1,67	3,80	3,41	2,60	—	—	4,35	7,35	6,0	12,0	2,6	14,0	—	—	—

*Hydrochloride.

The values obtained for the vicinal constants (10.0, 10.0, and 2.5 Hz) show conclusively that the rings are trans-fused.

In the spectrum of the ketone (II), the signal for the 2-H proton occurs as a multiplet, and that for the protons at $C_{(3)}$ as a doublet with a separation at 7.0 Hz. Decoupling from the methyl protons converted the multiplet for the 2-H proton into a triplet with the same separation. Such a $^1H-\{^1HCH_3\}$ spectrum could arise if, in the 2-H, 3-H proton system masking of spin coupling occurred, when the chemical shifts of the protons at $C_{(3)}$ coincide, and the constants $^3J_{2\text{-}H\text{-}3H_a}$ and $^3J_{2H\text{-}3H_e}$ are different [2]. The observed separation is half the sum of these constants.

Degeneration of the spectrum of the ketone (II) occurs when methanol is used as the solven in place of chloroform, the doublet for the $C_{(3)}$ protons and the multiplet for the 2-H proton breaking down into a greater number of components. The addition to a solution of the ketone (II) in $CDCl_3$ of its hydrochloride, a donor of acidic protons, results in greater changes in the spectrum. Since protonation is a rapid and reversible reaction, the spectra of the mixture are averaged out, their general appearance depending on the amount of hydrochloride added [3]. As the concentration of the hydrochloride is increased, the doublet is converted into two quartets at a distance of 0.60 ppm, with $^2J_{3\text{-}H_a-3\text{-}H_e}=14.0$, $^3J_{2\text{-}H-3\text{-}H_a}=12.0$, $^3J_{2\text{-}H-3\text{-}H_e}=2.6$ Hz. The same constants are seen in the spectrum of the hydrochloride. The values found for the couplin constants indicate that the 2-H proton has the axial configuration, and consequently the methyl group in the ketone (II) is equatorially oriented. It is interesting that interference with the random equivalence of the protons at $C_{(3)}$ evidently results from bonding of the n-pair of the nitrogen. Separate signals for the angular protons in (II) were not seen in the spectrum of the hydrochloride, nor in that of the free base. Addition of the paramagnetic shift reagent $Eu(Fod)_3$ (tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octandionato-europium) to the ketone (II) enables the 10- proton multiplet to be shifted to a resonance-free region, and it appears as a triplet (10.0 Hz) of doublets (3.0 Hz). Hence, the ketone (II), like the isomeric ketone (I), has transfused rings, and consequently, aminomethylation of phenylacetylene with paraformaldehyde and the trans-isomers of 2-methyldecahydroquinol-4-one does not result in configurational changes in the original skeleton of the aminoketone (see diagram).

Ethynylation in liquid ammonia in the presence of powdered KOH of the decahydroquinolone (I) gave a single acetylenic alcohol (III), whereas the ketone epimeric at $C_{(2)}$ gave a mixture of alcohols (IV) and (V), which were separated in the pure state [1]. Treatment of the alcohol (III-V) with a mixture of acetyl chloride and acetic anhydride gave the acetyl derivatives (VI-VIII). The PMR spectra of the alcohols and their acetates (Table 2) show that ethynylation under these conditions likewise results in no configurational changes in the original decahydroquinolone skeleton, and consequently (IV) and (V) are epimeric at $C_{(4)}$.

The orientation of the hydroxy group in alcohols (III-V) was established from the changes in the chemical shifts of the 2-H, 3-H_a, and 3-H_e protons following replacement of chloroform by pyridine as solvent. It is known [4] that in acetylenic alcohols of the piperidine and decahydroquinoline series in which the hydroxy group is axially oriented at $C_{(4)}$, pyridine causes considerable descreening of the axial proton or axial methyl at $C_{(2)}$. Descreening of the proton vicinal to the hydroxy-group increases when the dihedral angle between them decreases.

On the basis of these criteria, and from the Δδ values shown in Table 1, it may be concluded that the hydroxy-group is axially oriented in (III) and (V), and equatorially in (IV).

TABLE 2. Chemical Shifts and Coupling Constants of Protons in (III-VIII)

Compound	Solvent	δ, ppm									J, Hz						
		2-CH_3	2-H	3-H_a	3-H_e	9-H	N—CH_3	Ph	C≡CH	$OCOCH_3$	2-H—2-CH_3	2-H—3-H_a	2-H—3-H_e	3-H_a—3-H_e	9-H—10-H	9-H—8-H_a	9-H—8-H_e
III	$CDCl_3$	1,33	3,43	2,31	1,90	—	3,63	7,23	2,36	—	7,0	5,2	1,6	14,2	—	—	—
III	C_5D_5N	1,55	3,41	2,41	2,10	—	3,51 3,82	7,25	3,05	—	7,0	5,0	1,8	13,5	—	—	—
III*	$CDCl_3$	1,68	4,01	2,66	2,25	3,52	4,20	7,36	2,65	—	7,0	5,2	2,2	14,5	9,5	9,5	2,5
IV	$CDCl_3$	1,15	2,99	1,64	2,00	—	3,80	7,24	2,47	—	6,0	11,5	2,7	12,0	10,0	10,0	3,0
IV	C_5D_5N	1,07	3,25	1,90	2,28	2,75	3,83	7,27	3,25	—	6,0	11,7	2,7	11,7	10,5	10,5	3,5
IV*	$CDCl_3$	1,56	3,83	2,42	2,24	3,30	4,29	7,41	2,65	—	6,5	12,5	—	13,0	—	—	—
V	$CDCl_3$	1,11	2,98	1,77	1,98	2,55	3,80	7,23	2,36	—	6,2	12,5	2,0	13,3	10,0	10,0	2,5
V	C_5D_5N	1,07	3,35	1,94	2,22	2,93	3,85	7,28	3,05	—	6,5	11,5	2,7	13,0	10,5	10,5	2,5
V*	$CDCl_3$	1,50	3,91	2,15	2,38	3,47	4,28	7,40	2,62	—	6,5	12,0	1,5	13,0	—	—	—
VI	$CDCl_3$	1,20	3,42	3,15	2,91	—	3,65	7,24	2,49	2,01	7,0	5,2	2,2	14,8	—	—	—
VI*	$CDCl_3$	1,51 1,16	3,98	2,82	3,11	—	4,23 4,20	7,36	2,62	3,25	6,7 6,0	5,2	2,0	15,7	9,0	9,0	2,5
VII	$CDCl_3$	1,13	3,05	2,44	2,83	—	3,78	7,25	2,59	1,98	6,0	11,0	2,2	11,5	—	—	—
VII*	$CDCl_3$	1,58	3,75	2,48	3,08	3,36	4,25	7,40	2,73	3,28	6,5	12,5	2,2	13,5	10,5	10,5	3,5
VIII	$CDCl_3$	1,09	2,74	—	2,90	—	3,77	7,26	2,49	1,98	6,5	13,0	1,5	13,7	10,0	10,0	2,5
VIII*	$CDCl_3$	1,57	3,37	2,65	3,15	3,37	4,29	7,35	2,67	3,22	6,5	12,7	2,5	14,5	—	—	—

*Hydrochloride.

TABLE 3. Changes in the Chemical Shifts of Protons at $C_{(2)}$ and $C_{(3)}$ in Alcohols (III-V) on Replacement of Chloroform by Pyridine as Solvent

Compound	Δδ, ppm				Orientation of substituent	
	2-H	2-CH_3	3-H_a	3-H_e	OH	C≡CH
III	−0,02	0,23	0,10	0,20	*a*	*e*
IV	0,26	−0,08	0,26	0,28	*e*	*a*
V	0,36	−0,04	0,17	0,24	*a*	*e*

This conclusion is confirmed by the values of the chemical shifts of the ethynyl group protons in the acetylenic alcohols (III-V) and their acetates (VI-VIII) in $CDCl_3$ (Table 2). The proton of the axial ethynyl group in (IV) and (VII) resonates at lower field (by approximately 0.1 ppm) than the proton of the equatorial group in (III), (V), (VI), and (VIII) [4, 5]

The orientation of the hydroxy-group in saturated tertiary six-membered alcohols is normally established from the ν_{OH} value and the shape of the ν_{C-O} band in their IR spectra, assuming that the ν_{OH} frequency of the axial group is some 2-7 cm^{-1} greater than that of the equatorial group, and that the shape of the ν_{C-O} band for the axial acetate is more complex than that for the equatorial compound [6]. In the spectrum of the acetylenic alcohol (V) in CCl_4 ($c = 2 \cdot 10^{-3}$ mole/liter), absorption is seen at 3626 cm^{-1}, and in the spectrum of the epimeric alcohol (IV), the absorption occurs at 3623 cm^{-1}. These findings are in accordance with their structures as established by PMR. The shape of the ν_{C-O} band of the equatorial acetate (VII) was found to be more complex than in the axial acetates (VI) and (VIII). We therefore have an exception to the "acetate rule" [6], and its use to determine the configuration of epimeric pairs of alcohols requires due care.

To establish the structures of the acetylenic alcohols (III-V), we have also employed direct synthesis. They were obtained in satisfactory yields by aminomethylating phenylacetylene with the appropriate isomers of 2-methyl-4-ethynyl-4-hydroxydecahydroquinoline (IX-XI) of known configuration [7, 8]. The reactions were carried out in dry dioxane in the presence of catalytic amounts of copper(I) chloride, using a tenfold excess of phenylacetylene, at 95°C. Alcohols (III-V), obtained from the noramines (IX-XI), gave no depression of melting point on admixture with the samples obtained for ketones (I) and (II).

The establishment of the structures of the acetylenic alcohols (III-V) and the ratios of these in the reaction mixture [1] enables conclusions to be drawn concerning the stereochemistry of the ethynylation of the ketones (I) and (II). The reaction of (I) with acetylene is strictly stereospecific, giving only one isomer, the acetylenic alcohol (III) which has an equatorial ethynyl group. In our view, this is the result of steric hindrance by the axial methyl group at $C_{(2)}$, as in the case of the noraminoketone [8].

Ethynylation of the ketone (II), with an equatorial methyl group at $C_{(2)}$, results in the formation of both the theoretically possible acetylenic alcohols (IV) and (V), with a slight preponderance (55%) of the epimer (V) with an equatorial ethynyl group. This is somewhat in conflict with the stereochemistry of the ethynylation of the noraminoketone [8], with an equatorial methyl group. It is, however, necessary to bear in mind that ethynylation of the latter ketone was effected by the Favorskii reaction in ether solution, whereas the ethynylation of (II) was carried out in liquid ammonia. This may also be the reason for the difference in the stereochemical directivity of the addition of acetylene to the carbonyl group of the N-substituted compound (II) and of the noraminoketone [8].

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrometer in CCl_4 solution and KBr disks (KCl in the case of hydrochlorides), and PMR spectra on a Tesla BS 487 C (80 MHz) spectrometer, internal standard HMDS, δ scale. Thin layer chromatography was carried out and the course of the reactions followed on Silufol UV-254 plates in the system hexane–acetone (2:1) with the addition of 1% ammonia, viewed in UV light.

Stereoisomeric 1-(3-Phenyl-2-propynyl)-2-methyl-4-ethynyl -4-acetoxydecahydroquinolines (VI-VIII). A. A mixture of 2 g (6 mmole) of the hydrochloride of the aminoalcohol (III) and 20 ml (0.2 mole) of acetic anhydride was kept at 50-55°C until solution was complete, then 10 ml (0.14 mole) of acetyl chloride was added, the mixture boiled for 2 h, the solvent evaporate and the residue dissolved in 20 ml of water. The solution was acidified with hydrochloric acid to pH 1, and extracted with diethyl ether (4 × 50 ml). The aqueous solution as treated in the cold with saturated potassium carbonate solution to pH 10, then extracted with ether (5 × 50 ml), the extract dried over sodium sulfate, the solution concentrated to a volume of 30 ml, and ethereal HCl added to pH 2. The solid which separated was filtered off and recrystallized to give 1.68 g (75%) of (VI) hydrochloride, mp 190-191°C (from alcohol/ether), R_f 0.60. IR spectrum (KCl): 1234, 1242, 1255 (ester C–O), 2120 (C≡C), 3310 cm^{-1} (≡C–H). Found: C 71.3; H 7.4; Cl 9.1%. $C_{23}H_{27}NO_2 \cdot HCl$. The base (VI) was obtained from the hydrochloride in the usual way, mp 126-127°C (from hexane). Found: C 79.1; H 7.9; N 4.3%. $C_{23}H_{27}NO_2$. Calculated: C 79.1; H 7.8; N 4.0%.

B. Similarly, from 2 g (6 mmole) of (IV) hydrochloride was obtained 1.48 g (66%) of (VII) hydrochloride, mp 116-118°C (from diethyl ether by slow evaporation), R_f 0.75. IR spectrum (KCl): 1240, 1250, 1280 (ester C–O), 2120 (C≡C), 3322 cm^{-1} (≡C–H). Found: C 71.4; N 3.6%. $C_{23}H_{27}NO_2 \cdot HCl$. Calculated: C 71.6; N 3.6%. (VII) free base, mp 85-87°C (from hexane). Found: C 78.9; H 7.8%. $C_{23}H_{27}NO_2$. Calculated: C 79.1; H 7.8%.

C. As for (VI), from 2 g (6 mmole) of (V) hydrochloride there was obtained 1.79 g (80%) of (VIII) hydrochloride, mp 219-220°C (from ether/alcohol), R_f 0.80. IR spectrum (KCl): 1235, 1276 (ester C–O), 2122 (C≡C), 3320 cm^{-1} (≡C–H). Found: C 71.6; H 7.4%. $C_{23}H_{27}NO_2 \cdot HCl$. Calculated: C 71.6; H 7.3%. (VIII) free base, mp 143-145°C (from acetone). Found: C 79.1; H 7.8%. $C_{23}H_{27}NO_2$. Calculated C 79.1; H 7.8%.

Stereoisomers of 1-(3-Phenylprop-2-ynyl)-2-methyl-4-ethynyl-4-hydroxy-decahydroquinoline (III-V). A. A mixture of 1 g (5.7 mmole) of (IX) (mp 127-128°C [8, 9]), 0.24 g (7.2 mmole) of paraformaldehyde, 5.27 g (57 mmole) of phenylacetylene, and 0.1 g of freshly-prepared CuCl in 30 ml of dry dioxane was stirred vigorously for 1 h at 97°C, cooled to 10°C, acidified with dilute hydrochloric acid (1:1) to pH 1, and extracted with diethyl ether (4 × 50 ml). The acid aqueous solution was treated at 20°C with 25% aqueous ammonia, and extracted with ether (5 × 50 ml). The combined extracts were dried over magnesium sulfate and the solvent removed to give 0.6 g (40%) of (III), mp 139-140°C (from ethyl methyl ketone).

B. Similarly, from 1 g (5.7 mmole) of the noraminoalcohol (X), mp 127-128°C [7, 8] was obtained 0.9 g (60%) of (IV), mp 125-126°C [1] (from benzene/light petroleum).

C. Similarly, from 1 g (5.7 mmole) of the noraminoalcohol (XI) was obtained 0.84 g (56% of (V), mp 144-145°C [1] (from benzene/light petroleum).

The IR spectra, R_f values, and melting points of the N-substituted alcohols (III-V) were identical with those reported in [1]. The acetylenic alcohols (III-V) and their hydrochlorid gave no depression of melting point on admixture with authentic samples, obtained as describe in [1].

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