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SYNTHESIS AND STERIC STRUCTURE OF STEREOISOMERIC 2-*p*-NITROPHENYLPERHYDROQUINAZOLIN-4-ONES

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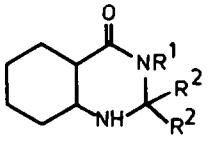
Abstract - Ethyl *cis*- and *trans*-2-aminocyclohexanecarboxylate (4) were used as starting material to prepare (*r*-4a,*t*-2,*t*-8a)-, (*r*-4a,*c*-2,*c*-8a)- and (*r*-4a,*t*-2,*c*-8a)-2-*p*-nitrophenylperhydroquinazolin-4-one and their 3-methyl-substituted derivatives in stereospecific or stereoselective syntheses. The relative configurations of the quinazolones were assigned via DNOE measurements. Crystal structure determinations of *cis*-7a and *cis*-8a were also performed by X-ray diffraction.

The quinazolin-4-one moiety is present in a number of various alkaloids.[2] The chemistry and pharmacology of these derivatives have been thoroughly investigated.[2-4] In spite of this, little attention has been paid to the partially and fully saturated analogues. Synthesis of the unsubstituted *cis*- and *trans*-fused perhydroquinazolin-4-ones has been reported by Armarego,[5] but without NMR characterization. We recently reported[6] the preparation of 2,2-disubstituted perhydroquinazolinone diastereomers 1, by reacting the *cis*- and *trans*-2-aminocyclohexanecarboxamides with ketones.[3] In another simple preparation of perhydroquinazolinones, also starting from the 2-aminocyclohexanecarboxamides, but using the Leuckart reaction, 1-methyl-3-hydroxymethylperhydroquinazolin-4-ones were formed.[7]



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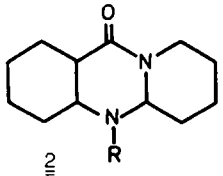

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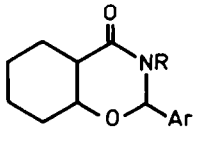

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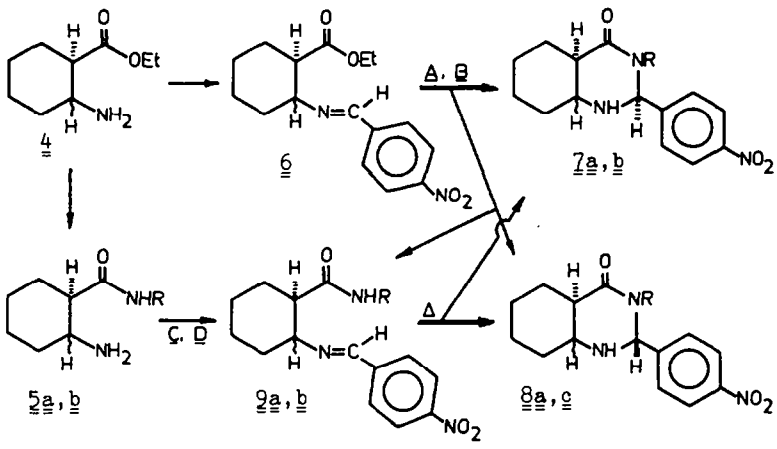
The synthesis and stereochemistry of the closely related analogues perhydropyrido[2,1-*b*]quinazolin-11-ones[8,9] 2 and 1,3-perhydrobenzoxazines[10] 3 have likewise been thoroughly studied. The syntheses were performed by starting from the ethyl *cis*- and *trans*-2-aminocyclohexanecarboxylate[11] 4 and from the corresponding cyclohexane carboxamides[5,6,11] 5a,b, similarly as in the synthesis of the aromatic analogues.[12]

All the discussed compounds are racemates. The Figures show only the enantiomer in which, in accordance with the IUPAC rules,[13,14] the C-1 atom in the starting amino acids and the corresponding carbon atom in the products have the *R* configuration. The product distribution was always determined by means of 400 MHz NMR spectroscopy, through the integrals of the well-separated C-2 and methine signals (Fig. 1). In the NH (a) and NCH_3 (b) series, no significant difference in the isomer distributions was observed in the crude products.



From:* (Method)	Product ratios 7	8	9
c-6 (A or B)	5	2	3
t-6 (A or B)	-	9	1
c-5 (C)	-	2	8
(D)	2	3	5
t-5 (C)	-	7	3
(D)	-	8	2

* c = cis, t = trans

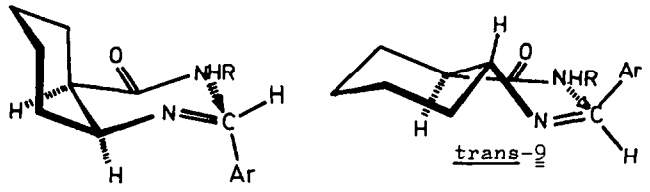
cis or trans; a: R = H, b: R = Me

Figure 1

In the reaction of the trans or cis 4 with p-nitrobenzaldehyde at room temperature, the E benzylidene derivative 6 was formed in nearly quantitative yield. From the cis benzylidene derivative 6, the ring closure with ammonia or methylamine took place stereoselectively: the main product was the 7a,b all cis, while the minor ring product 8a,b had the (r-4a,t-2,c-8a) relative configuration. From the trans-6 with amines 8a,b having the (r-4a,t-2,t-8a) relative configuration were formed stereospecifically. Besides the above ring closure products, the cis and trans carboxamides 9a,b were also detected in the crude product.

The esters 4, gave amides 5,[5,6,11] which reacted with p-nitrobenzaldehyde yielding a mixture of 7 and 8 (Scheme 1).

The stereospecificity of the ring closure by Methods C and D may be explained by examining the structures of 9a,b. In the case of the diequatorially substituted E-trans derivative the formation of merely a single product can be expected (Fig. 2). At room temperature, the cis carboxamides 9a,b predominantly favour the N-inside conformation ($\mathcal{E}J_{2-H}$ = 13.5 Hz) and hence only the formation of a single diastereomer, cis-8a,b, was observed. In boiling ethanol, products cis-7 and cis-8 are formed simultaneously, presumably because E-Z isomerization of cis-9a,b took place (Fig. 2).



cis-9 trans-9

Figure 2

Since the amidation of 4 with ammonia or methylamine is slower than the ring closure of the benzylidene ester 6, the formation of amide 9 is only a side-reaction in the latter case. The main route is amine addition to the C=N double bond, followed by nucleophilic attack on the ester carbonyl. Consequently, formation of the thermodynamically more stable 2-p-nitrophenylperhydroquinazolin-4-ones 7a,b prevails.

STRUCTURAL INVESTIGATION. In principle, in all of the ring closure reactions two C-2 epimeric products could be formed. However, in the trans series the formation of only a single product was always observed. The high value (25 Hz) of $\mathcal{E}J_{8a-H}$ provides evidence of the diequatorial ring junction. The relative configurations of the products were confirmed by DNOE measurements. Saturation of the H-2 signals at 5.56 and 5.34 ppm resulted in higher intensities for the H-8a and the aromatic

proton signals, in agreement with the (r-4a,t-2,t-8a) relative configuration (Fig. 3). In the related trans-annelated 1,3-perhydrobenzoxazinones the same relative configuration was demonstrated by NMR spectroscopy[10] and X-ray diffraction.[15]

The relative configurations of cis-7a,b and 8a,b at C-2 were determined from DNOE measurements. With 7a,b, saturation of the H-2 signal (at 5.49 and 5.30 ppm) resulted in NOE enhancements for H-8a and the aromatic hydrogens. With the corresponding C-2 epimeric compounds (8a,b), NOE enhancement was found not for H-8a, but for the aromatic lines, and partly for the broad peaks of the aliphatic hydrogens at 1.4-1.9 ppm.

The cis-fused compounds 7a,b and 8a,b can in principle exist in two stable chair-(half-chair) conformations, i.e. the N-inside and N-outside forms (Fig. 3). The $\measuredangle J_{8a-H}$ coupling (10.5 Hz) shows that 7a,b exists predominantly in the N-inside conformation. Similarly, the $\measuredangle J_{8a-H}$ coupling (16.3 and 14.0 Hz) allow the estimation that 8a,b are approximately 3:2 and 3:1 mixtures of the N-inside and N-outside conformation, respectively (Fig. 3). Katritzky et al.[16] reported that the nearly analogous cis-perhydroquinazoline-2,4-dione exists in an about 1:1 mixture of the N-inside and N-outside forms.

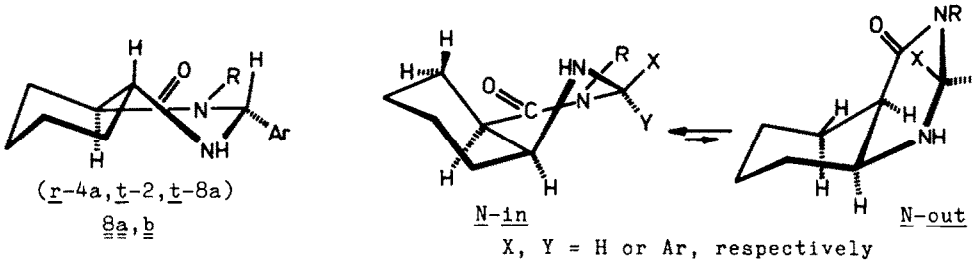


Figure 3

X-ray analysis of perhydroquinazolinones cis-7a and cis-8a

Figure 4 shows a perpendicular view of the structures. The cis-7a assumes two forms (I and II), computed from the final relative coordinates given with their e.s.d.'s in Table 1. Despite the conclusions inferred above from the NMR studies, N-inside is the predominant conformation for both cis-7a and cis-8a in the crystalline state. This is expressed quantitatively by the torsion angle N(1)-C(8a)-C(4a)-C(5), which indicates the axial orientation of N(1) in each structure [74.6(4)° for cis-7aI, 74.8(4)° for cis-7aII and 77.1(2)° for cis-8a]. It is worth noting that the conformers I and II of cis-7a do not exhibit any significant difference. The greatest difference is shown by the rotation about the C(12)-N(16) bond, expressed by the torsion angle C(13)-C(12)-N(16)-O(18): 15.7(5)° for I and -6.4(5)° for II. In cis-8a this torsion angle is -1.6(3)°.

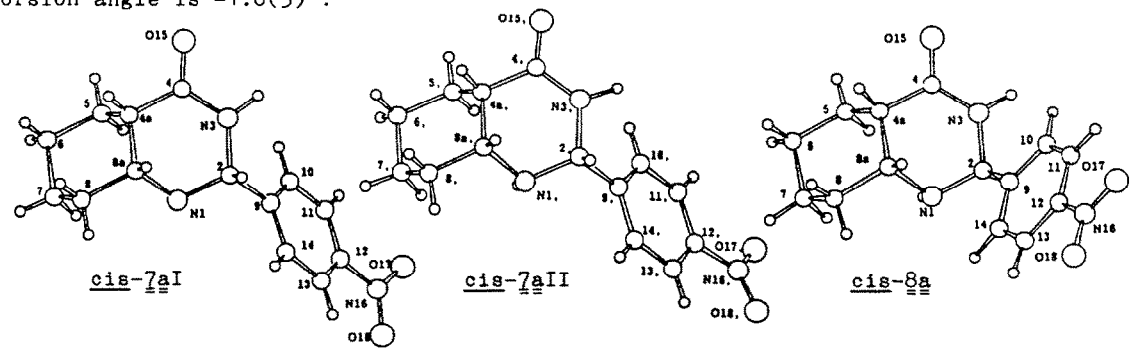


Fig. 4. Perspective views of the molecules cis-7aI, 7aII and 8a with atomic labelling. The bare numbers are for carbon unless indicated otherwise. Hydrogen atoms are shown but not labelled.

Table 1. Relative atomic coordinates ($x10^4$) for non-hydrogen atoms for cis-7aI, cis-7aII and cis-8a with their e.s.d.'s

Atom	cis-7aI			cis-7aII			cis-8a		
	x/a	y/b	z/c	x/a	y/b	z/c	x/a	y/b	z/c
N(1)	-758(3)	-1199(1)	1111(1)	5896(3)	5786(1)	9235(1)	5426(1)	-4646(1)	2005(1)
C(2)	901(3)	-786(1)	1346(1)	4206(3)	6158(1)	8989(1)	6374(1)	-2974(1)	1634(1)
N(3)	1210(3)	-932(1)	1963(1)	3714(3)	5847(1)	8411(1)	5316(1)	-1813(1)	975(1)
C(4)	551(3)	-1591(1)	2245(1)	4359(3)	5153(1)	8172(1)	3467(1)	-1956(1)	913(1)
C(4a)	-924(3)	-2120(1)	1952(1)	5885(3)	4687(1)	8495(1)	2321(1)	-3398(1)	1576(1)
C(5)	-2841(3)	-1865(1)	2184(1)	7780(4)	4855(2)	8217(1)	1967(1)	-4901(1)	856(1)
C(6)	-4412(4)	-2374(2)	1904(1)	9358(4)	4399(2)	8541(1)	919(2)	-6509(2)	1441(1)
C(7)	-4410(4)	-2270(1)	1259(1)	9446(4)	4644(2)	9165(1)	2082(2)	-7366(2)	2196(1)
C(8)	-2522(4)	-2515(1)	1014(1)	7581(4)	4482(1)	9449(1)	2376(2)	-5908(2)	2947(1)
C(8a)	-869(3)	-2067(1)	1300(1)	5933(3)	4888(1)	9137(1)	3328(1)	-4199(1)	2420(1)
C(9)	801(3)	126(1)	1201(1)	4368(3)	7091(1)	8990(1)	6708(1)	-1824(1)	2526(1)
C(10)	453(3)	740(1)	1605(1)	4544(3)	7548(1)	8486(1)	6847(2)	89(1)	2430(1)
C(11)	324(4)	1565(1)	1438(1)	4603(4)	8405(1)	8496(1)	7186(2)	1123(1)	3227(1)
C(12)	519(3)	1753(1)	869(1)	4460(3)	8793(1)	9018(1)	7418(1)	197(1)	4115(1)
C(13)	874(4)	1162(1)	457(1)	4346(4)	8368(1)	9525(1)	7338(2)	-1713(2)	4233(1)
C(14)	1039(3)	348(1)	635(1)	4303(4)	7512(1)	9507(1)	6868(2)	-2717(1)	3431(1)
O(15)	1074(2)	-1749(1)	2738(1)	3765(3)	4909(1)	7701(1)	2729(1)	-985(1)	301(1)
N(16)	357(3)	2622(1)	685(1)	4376(3)	9698(1)	9027(1)	7768(1)	1286(1)	4968(1)
O(17)	421(3)	3156(1)	1058(1)	4582(3)	10073(1)	8581(1)	7864(2)	2971(1)	4846(1)
O(18)	134(3)	2772(1)	183(1)	4043(4)	10045(1)	9475(1)	7932(1)	463(1)	5756(1)

Within experimental error, the corresponding bond lengths and angles agree well with each other, showing the excellent internal consistency of the two structure determinations. In each structure the lone pair of N(3) is delocalized toward the oxo group, resulting in a strong N(3)-C(4) multiple bond [1.341(3) Å]. It is likely that there is a weak through-conjugation between the N(1)-C(2) and N(3)-C(4) bonds, as shown by the N(1)-C(2) mean bond length of 1.451(3) Å. The N(3)-C(2) and N(1)-C(8) bond lengths indicate N(sp^3)-C(sp^3) single bonds. The only visible difference in the bond angles pertaining to the hetero ring can be seen at C(2). The axial p-nitrophenyl group in cis-8a is accompanied by a 1.4° smaller N(1)-C(2)-N(3) angle than for the equatorial group in cis-7a. Apart from the different configurations at C(2), the epimers exhibit only small difference in pucker, as shown by the Cremer and Pople[17] puckering parameters:

	cis-7aI	cis-7aII	cis-8a	
Q	0.279(3)	0.322(3)	0.373(2) Å	Each has a half-chair N(3)-C(4)-monoplanar conformation, with increasing puckering amplitude Q from cis-7aI to cis-8a.
φ	326.1(6)	322.2(5)	331.9(2)°	
θ	38.6(4)	44.6(4)	50.7(2)°	

In cis-7a, the molecules are bound together in dimers by intermolecular hydrogen-bonds. In each dimer, two symmetry-independent molecules are linked by a pair of hydrogen-bonds of NH...O type. In cis-8a, the centre of symmetry-related pair of molecules form dimer associates with the hydrogen-bond parameters.

		D...H	H...A	DH...A
cis-7a	N(3)-H(3).....O(15')	2.978(2)	2.05(2) Å	173(2)°
	N(3')-H(3')...O(15)	2.827(3)	1.86(3) Å	179(2)°
cis-8a	N(3)-H(3).....O(15)	2.844(2)	1.96(2) Å	174(1)°

EXPERIMENTAL

M.p.s were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded in $CDCl_3$ solution on a JEOL GX 400 FT spectrometer, at ambient temperature, using TMS as internal standard.

Ethyl N-(p-nitrobenzylidene)-trans- (6) and cis-2-aminocyclohexanecarboxylate (12)

Ethyl cis- or trans-2-aminocyclohexanecarboxylate (4) (342 mg, 2 mmol) was dissolved in 15 ml ethanol, and p-nitrobenzaldehyde (302 mg, 2 mmol) was added. After the mixture was left to stand for 2 h at room temperature, the solvent was evaporated off and the yellow oily product was used without further purification.

Preparation of perhydroquinazolinones 7 and 8

(A) Ring closures of 6 with NH_3. — The benzylidene derivative 6 (0.3 g, 1 mmol) was left to stand in a solution of ammonia in methanol (10 ml, 20% ammonia content) for 48 h. The solvent was then evaporated off.

(B) Ring closures of 6 with CH_3NH_2. — The benzylidene derivative 6 (0.3 g, 1 mmol) was dissolved in a mixture of ethanol (5 ml) and aqueous methylamine (40% methylamine content) (10 ml) and left to stand for 48 h. The solvent was then evaporated off.

(C) At room temperature. — The 2-aminocyclohexanecarboxamide 5a,b (1 mmol) was dissolved in ethanol (10 ml), and p-nitrobenzaldehyde (151 mg, 1 mmol) was added. After the mixture was kept for 1.5 h at room temperature, the solvent was evaporated off below 40 °C at reduced pressure.

(D) In boiling ethanol. — The reaction mixture described in method (C) was refluxed for 5 h before the evaporation of the solvent.

The product distributions, determined from ^{1}H NMR spectra taken immediately after evaporation of the solvent, are given in Fig. 1. The Schiff bases 9a,b were not separated in pure form, but the characteristic signals were readily recognized from the ^{1}H NMR spectra. The perhydroquinazolinones were separated from the crude product in a spectroscopically and analytically pure form by fractional crystallization followed by TLC on a preparative plate (Merck), with benzene-ethanol as eluent (4:1).

Table 2. Analytical data and selected ^{1}H NMR chemical shifts (ppm) for perhydroquinazolinone stereoisomers

Compound	M.p. (°C)	Crystallization solvent	Calcd./Found (%) C	H	N	Formula (M.w.)	δ2-H s(1H)	δ4a-H m(1H)	δ8a-H m(1H)
cis-7a	183-185	ethanol	61.07	6.22	15.26	$C_{14}H_{17}N_3O_3$	5.49	2.37	3.39
			60.91	6.44	15.26	(275.31)			
cis-7b	179-181	ethyl acetate	62.27	6.62	14.52	$C_{15}H_{19}N_3O_3$	5.30	2.46	3.38
			62.03	6.77	14.76	(289.32)			
cis-8a	169-170	ethyl acetate	61.07	6.22	15.26	$C_{14}H_{17}N_3O_3$	5.62	2.49	3.11
			61.28	6.52	15.39	(275.31)			
cis-8b	153-154	ether	62.27	6.62	14.52	$C_{15}H_{19}N_3O_3$	5.39	2.49	3.09
			62.45	6.40	14.20	(289.32)			
trans-8a	187-188	ethanol	61.07	6.22	15.26	$C_{14}H_{17}N_3O_3$	5.56	2.40	2.78
			61.31	6.34	15.15	(275.31)			
trans-8b	170-171	ethyl acetate	62.27	6.62	14.52	$C_{15}H_{19}N_3O_3$	5.34	2.46	2.75
			62.31	6.73	14.66	(289.32)			

Crystal structure determination of cis-7a

Crystal data: $C_{14}H_{17}N_3O_3$, M_r = 275.31, monoclinic, space group $P2_1/c$, a = 7.131(2), b = 16.154(2), c = 23.368(3) Å, β = 91.45(2)°, U = 2691(2) Å^3, D_c = 1.36 g.cm^{-3}, Z = 8 (two molecules in the asymmetric unit), F(000) = 1168, μ = 7.6 cm^{-1} for Cu-K_α radiation (λ = 1.54184 Å).

Intensities of 4753 unique reflections were collected on an Enraf-Nonius CAD-4 diffractometer in the range $1.5 < \theta < 75.0$ by an ω-2θ scan, using graphite monochromated Cu-K_α radiation. Cell constants were determined by least squares refinement of 25 reflections. Three standard reflections were monitored every hour and showed no significant decrease during the exposure. After data reduction, 3697 reflections with $I > 3.0\sigma(I)$ were taken as observed. The phase problems were solved

by direct methods using the MULTAN 82 program.[18] In the course of the isotropic least squares refinement of the positional parameters on non-hydrogen atoms, an empirical absorption correction was calculated with the DIFABS[19] program. The minimum and the maximum corrections were 0.861 and 1.479. The fractional coordinates of H atoms bound to carbon atoms were generated from assumed geometries, while those of the NH groups were located in a difference Fourier map. The hydrogen positions together with their temperature factors were refined in isotropic mode in the final stage of the anisotropic treatment of the non-hydrogen atoms. Final R = 0.047, R_w = 0.069, R_{tot} = 0.067, S = 5.85. The highest peak in the final difference Fourier map was 0.26(5) e.Å^{-3}, (Δ/σ) max = 0.12. Scattering factors were taken from standard tables.[20] All calculations were performed on a PDP 11/34 minicomputer with the use of the SDP system of Enraf-Nonius with local modification.

Crystal structure determination of cis-8a

Crystal data: $C_{14}H_{17}N_3O_3$, M_r = 275.31, triclinic, space group $P\bar{1}$, a = 7.076(1), b = 7.182(1), c = 13.334(1) Å, α = 88.56(1), β = 77.18(1), γ = 85.23(1), U = 658.4(2) Å^3, D_c = 1.39 g.cm^{-3}, Z = 2, F(000) = 292, μ = 7.8 cm^{-1} for Cu-K_α radiation (λ = 1.54184 Å).

Data collection, structure determination and refinement were basically similar as for cis-7a. Of 2691 unique reflections, 2464 were taken as observed with $I > 3.0\sigma(I)$. MULTAN 82, minimum and maximum absorption corrections: 0.803 and 1.359. The H positions were refined in isotropic mode. Full matrix refinement. Final R = 0.051, R_w = 0.091, R_{tot} = 0.054, S = 4.13. The highest peak in the final difference Fourier map was 0.22(5) e.Å^{-3}, (Δ/σ) max for H atoms 0.74.

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