SATURATED HETEROCYCLES, PART 257*. PREPARATION AND STRUCTURE OF PARTIALLY SATURATED ISOINDOLO[1,2-*b*]- AND -[2,1-*a*]QUINAZOLINONES

Pál Sohár[a], Géza Stájer[b], Angela E. Szabó[b], József Szúnyog[c] and Gábor Bernáth[a]

[a]Department of General and Inorganic Chemistry, Loránd Eötvös University, POB 32, H-1518 Budapest-112, Hungary; [b]Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, POB 121, H-6701 Szeged, Hungary; [c]EGIS Pharmaceuticals, POB 100, H-1475 Budapest, Hungary

Abstract – Through the reactions of 2-carboxybenzaldehyde (**1**) with *cis*- or *trans*-2-amino-1-cyclohexylmethylamine (**2a,b**) or *cis*- or *trans*-2-amino-4-cyclohexenyl-1-methylamine (**2c,d**), the partially saturated isomeric isoindolo[1,2-*b*]- (**3, 4, 6-8**) and -[2,1-*a*]quinazolinones (**5**) were obtained. After separation, the structures of products (**3-8**) were established by NMR methods, including 2D-HSC DNOE and DEPT measurements. From the *cis* **2a**, two linearly *C/D cis*-fused and one angularly *C/D trans*-fused tetracycles were formed.

Our earlier studies on the syntheses of saturated or partially saturated heterocycles from aroyl(bi)-cycloalkanecarboxylic acids[1,2] prompted us to prepare new condensed tetracyclic systems. In the present experiments, 2-carboxybenzaldehyde (**1**) as starting synthon reacted with cyclic diamines in which one of the functional groups was bound directly to a cyclohexane/ene ring, and the other indirectly through a methylene group. Platinum derivatives of diamines (**2a-d**) have antitumour effects.[3] **2a-d** used in the present experiments differ from the cyclic 1,3-amino alcohols applied previously in that the ring closures involve two amino groups of similar nucleophilicities. Hence, the formation of structurally isomeric heterocycles with linearly or angularly fused ring systems can be expected. Additionally, isomers can be formed that differ in the mutual positions of the annelational hydrogen in the *C/D* ring fusion and the hydrogen on the carbon between the two nitrogens. Furthermore, establishment of the stereostructure in the *C/D* ring fusion is essential, because *cis–trans* isomerization of the starting compounds often occurs during similar ring closures.[1]

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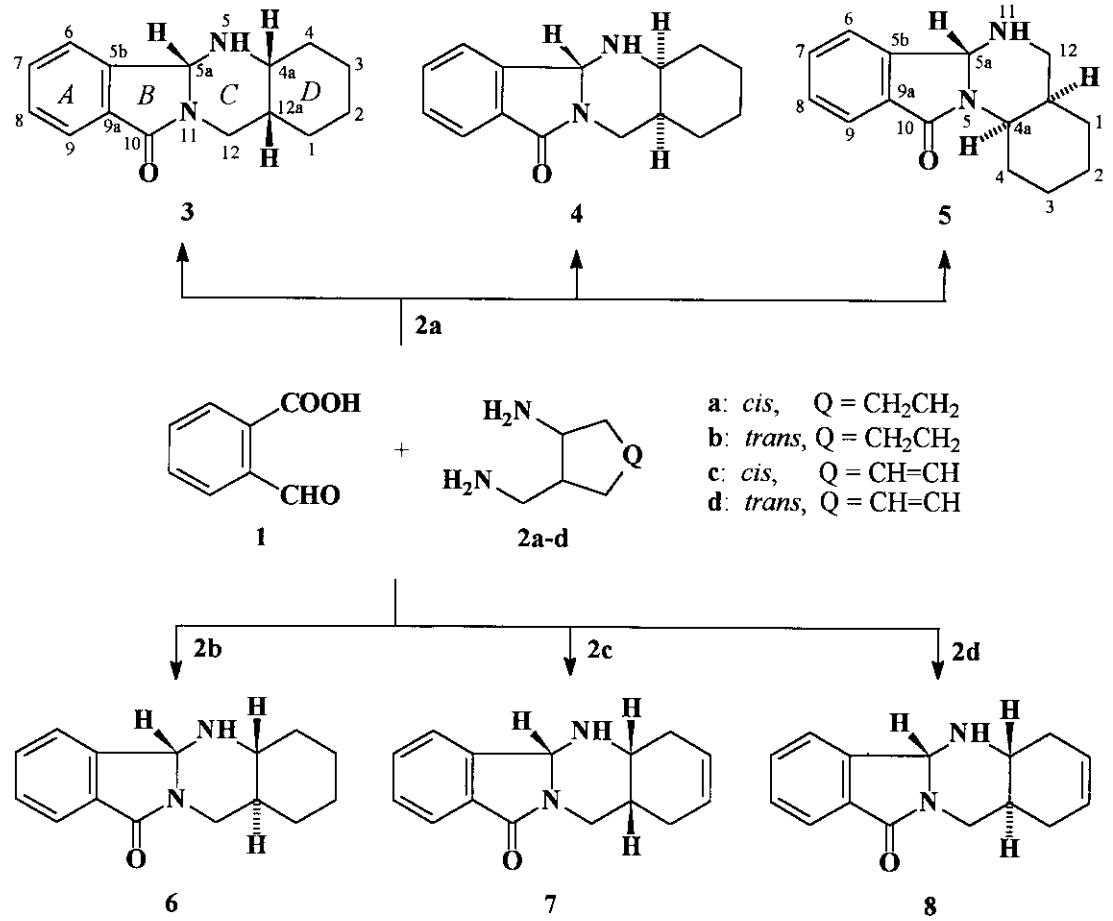
RESULTS

When boiled together in toluene, 2-carboxybenzaldehyde (**1**) and *cis*-2-amino-1-cyclohexylmethylamine (**2a**) yielded three products: the linearly condensed **3** and **4** and the angularly-fused **5** (Scheme), which were separated by HPLC. After isolation and crystallization, the structures of tetracycles (**3-5**) were established by NMR spectroscopy. The linearly-fused products (**3**) and (**4**) proved to be isoindoloquinazolinones containing an aromatic ring *A*, two condensed hetero rings and one terminal cyclohexane unit. Similar structural isomers have been prepared in the reaction of γ-aroylpropionic acid with **2a**.[2]



Scheme

In the reaction of **1** with *trans*-2-amino-1-cyclohexylmethylamine (**2b**), only one product (**6**) was isolated. Likewise, in the reactions of **1** with *cis*- or *trans*-2-aminocyclohex-4-enyl-1-methylamine (**2c** and **2d**), **7** and **8** were obtained. Similarly to **3** and **4**, these compounds are linearly condensed isoindoloquinazolinones. The spectral data given in Tables 1 and 2 indicate that the formation of these tetracyclic ring systems is straightforward.

The theoretically equally possible linearly or angularly condensed ring systems can be differentiated on the basis of the chemical shifts of the NC*H* and NCH_2 hydrogens. Due to the

anisotropic effect of the amide carbonyl,[4a] the former and one of the latter give significantly downfield shifted signals: 4.5 ppm (**5**) instead of 2.6-3.4 ppm (**3, 4, 6-8**), and 3.37 (**5**) instead of 4.15-4.43 ppm (**3, 4, 6-8**). Consequently, **3**, **4** and **6-8** contain the methylene group vicinal to the amide nitrogen, while in **5** the CH group is bound to this nitrogen atom. Hence, all these new compounds have linearly condensed skeletons, with the exception of **5**, which alone has an angular structure.

Table 1. Characteristic IR frequencies (cm^{-1})[a] and ^{1}H-NMR data (chemical shifts in ppm[b] and coupling constants in Hz) for compounds (**3-8**)*

	νNH band (broad)	νC=O band[c]	γCH band	CH_2 (Pos. 1-4) + CH (12a) 1-6 *m*'s (9H)	NCH_2[d] (2x1H)		NCH[e] *m* (1H)	NCHN *s* (1H)	ArH (benzene ring) *dd* (1H)[f]	(Pos. 6-8)[g]
3	3293	1677	735	~1.10 ~1.30[h,i] 1.50[h,i] ~1.65[j] 1.90	~3.35[h]	4.15	~3.35[h]	5.17	7.83	7.40–7.55
4	3600-2800[k]	1681	745	1.25–2.20	3.42	4.20	3.09	5.31	7.80	7.45–7.65
5	3455 3233	1659	753	1.50–2.00	2.90	3.37	4.50	5.26	7.85	~7.55
6	3280	1693	738	~1.05[h,l] 1.26[m] 1.41[m] 1.75[h,i] 1.82[n] ~2.60[h]	2.83	4.39	~2.6[h]	5.20	7.82	7.49 7.53 7.61
7	3428	1679	726	1.60-2.20[j] 2.50[n] 5.53[o]	~3.40[h]	4.22	~3.40[h]	5.23	7.83	7.45–7.65
8[p]	3262	1700		1.35 ~1.70[h,i] 2.11 2.39 5.60[o]	2.79	4.43	2.89	5.12	7.72	7.40 7.45 7.53

*For easier comparison of analogous spectral data, the numbering of **3** was used for all compounds in the text, the Scheme and the Tables. The correct numbering is given in the Experimental. Assignments were supported by DNOE measurements (except for **4**). [a]In KBr pellets; [b]In $CDCl_3$ solution at 500 MHz; $\delta_{TMS} = 0$ ppm; [c]Split, with the second maximum at 1665 (**4**) or 1681 (**6**); [d]*dd*, *J*: 13.4 and 0.7 (downfield signal of **3**, **5** and **7**, for **7** the *dd* is coalesced to a *t*), *J*: 13.3 and 5.5 (downfield signal of **4**, **6** and **8**), *J*: 13.8 and 4.0 (upfield signal of **5**), *J*: 13.0 and 11.2 (upfield signal of **6** and **8**), *t*, *J*: 13.0 (upfield signal of **4**); [e]Multiplicity: *td*, *J*: 12.6, 4.4 and 4.4 (**4**), ~9, ~5, ~5 (**5**), *dt*, *J*: 10.5, 10.5 and 5.5 (**8**); [f]Pos. 9 (*ortho* to CO substituent), $J_{ortho} \approx 7.4$; [g]Overlapping signals, separated to *t*, *t* and *d* for **6** and **8**, $J_{ortho} \approx 7.5$; [h]Overlapping signals; [i,l]Intensity 2H/3H; [j]In overlap with the NH signal, intensity 4H (**3**), 5H (**7**); [k]Diffuse band with a superimposed maximum at about 3270; [m]Quartet-like signal (1H) of the *axial* H in Pos. 2 or 3; [n]Doublet-like signal (1H) of the *equatorial* H in Pos. 2 or 3; [o]Singlet-like signal (2H) of the olefinic hydrogens in Pos. 2 and 3; [p]NH: 1.05 br *s* (1H).

The *cis*- or *trans*-condensed cyclohexane rings differ in the carbon shifts: due to the field effect[4b] (steric compression shift[5]), the sum of the carbon shifts ($\Sigma\delta C$) is significantly smaller for the *cis* compounds. $\Sigma\delta C$ is 184.5 (**3** and **5**) or 188.8 ppm (**4**) for the *cis*-annelated cyclohexanes, and 217.9 ppm for their *trans* counterpart **6** ($\Delta\Sigma\delta C \approx 32.0$ ppm). Similarly, $\Delta\Sigma\delta C$ is 22.6 ppm for the cyclohexene *cis–trans* pair **7** and **8**: $\Sigma\delta C$: 381.7 ppm (**7**) and 404.3 ppm (**8**). Hence, the *trans* annelation of the cyclohexane/ene ring in **6** and **8** and the *cis* annelation for **3-5** and **7** is unquestionable.

A further problem is to determine the relative positions of the isoindolone NC*H*N hydrogen and the annelational hydrogens of the partially or wholly saturated quinazoline ring. This was established by means of DNOE measurements.[4c,6]

On saturation of the isoindolone H-5a, responses from H-4a, H-12*ax* and H-6 were observed for **3** and **6-8**, which proves the steric proximity of the latter atoms to H-5a. The close location (1,3-*diaxial*) of H-4a and H-5a means the 4a*R**,5a*R**,12a*S** configuration for the *trans* compounds (**6**)

and (**8**), *i.e.* the *cis* position for H-4a and H-5a, and *trans* orientation for H-5a and H-12a (Scheme). In the *cis*-annelated **3** and **7**, the same NOE between H-4a and H-5a confirms the all-*cis* arrangement for H-4a,5a,12a, *i.e.* the configuration 4a*R**,5a*R**,12a*R**. In accordance, a significant field effect (upfield shift by 7.9 or 8.3 ppm) was observed for C-1 relative to C-4 in **3** and **7**, due to the steric interaction of the lone electron pair of N-5 and H-1*ax*. In consequence of the β-effect of N-5,[4d,7] the shift difference ΔδC-1,4 (which causes the downfield shift on C-4) is much smaller (3.9 and 3.3 ppm) in the *trans* isomers (**6**) and (**8**).

For **5**, irradiation of the H-5a signal in the DNOE experiment yielded no response of the H-5a multiplet. This proves the stereostructure containing the annelation hydrogens 4a,12a in the *trans* position with H-5a, *i.e.* the configuration 4a*R**,5a*R**,12a*R**.

Table 2. ^{13}C-NMR chemical shifts (δ, ppm[a]) for compounds (**3-8**)[b]

	CH_2 (1)	CH_2 (2)	CH_2 (3)	CH_2 (4)	CH (4a)	NCH (5a)	C-5b	CH (6)	CH (7)	CH (8)	CH (9)	C-9a	C=O (10)	CH_2 (12)	CH (12a)
3	23.1	24.9	19.3	31.0	52.1	71.1	142.4	122.5	131.0	128.9	123.1	132.5	165.4	43.9	34.1
4	28.3	20.5	24.6	26.0	53.9	65.9	143.2	122.8	131.3	129.2	123.5	133.0	165.4	38.1	35.5
5	28.2	20.5	25.0	26.5	48.8	68.0	142.4	122.9	131.3	129.3	123.4	133.0	165.0	45.0	35.9
6	29.6	25.8[c]	26.1[c]	33.5	59.7	72.1	143.0	123.3	131.8	129.7	123.9	133.5	165.4	44.6	43.2
7	22.9	122.9[c]	124.9[c]	31.2	50.9	71.3	142.2	122.6	131.2	129.0	123.2	132.3	166.0	43.4	29.9
8	29.0	125.5[c]	125.0[c]	32.3	55.0	71.2	142.5	122.8	131.4	129.2	123.4	132.9	164.7	43.7	37.5

[a]In $CDCl_3$ solution, at 125.72 MHz; $\delta_{TMS} = 0$ ppm; [b]Assignments were proved by DEPT, and for **3** and **6-8** also by 2D-HSC measurements; [c]Interchangeable assignments.

For **4**, the *cis* annelation of the cyclohexane and the vicinity of the methylene group with the amide-N was proved above. In the knowledge of the stereostructure of the diastereomer (**3**), which also contains a *cis*-annelated cyclohexane ring, for **4**, the only possible structure that remains is that in which the annelation hydrogens and H-5a are in the *trans* position. In comparison with **3**, the significant field effects on C-5a (5.2 ppm) and C-12 (5.8 ppm), due to the steric interaction with the 4-methylene group in the 1,3-*diaxial* position, are proof of this structure. The corresponding field effects on 2-CH_2 and 4-CH_2 are 4.4 and 5.0 ppm. Consequently, **4** has the configuration 4a*R**,5a*S**,12a*R**.

The above results support our previous finding:[1,2,8] in similar cyclizations, the *cis* or *trans* cyclic 1,3-amino alcohols or 1,3-diamines always react with retention of the configuration.

EXPERIMENTAL

The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature on a Bruker DRX 500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock, and TMS as internal standard. The standard Bruker microprogram DNOEMULT.AU to generate NOE was used with a selective pre-irradiation time. DEPT spectra[9] were run in a standard manner,[10] using only the θ = 135° pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-HSC spectra[11] were ob-

tained by using the standard Bruker pulse program HXCO.AU. IR spectra were run for KBr discs on a Bruker IFS-55v FT-spectrophotometer controlled by Opus 2.0 software. HPLC: ISCO system with two pumps, suitable for gradient elution; Chem. Research control system and data processing program. For the semipreparative separation, a 250 × 4 mm Nucleosil 5 Si column (250 × 16 mm) was used. Injected sample: 500 μl, of a 4% MeOH–THF (2 + 1) solution, detection at 270 nm.

10*H*,12*H*-1,2,3,4,4a,5,5a,12a-Octahydroisoindolo[1,2-*b*]quinazolin-12-ones (3, 4, 6), 6*H*,12*H*-1,2,3,4,4a,10b,11,12a-octahydroisoindolo[2,1-*a*]quinazolinone (5) and 10*H*,12*H*-1,4,4a,10b,-11,12a-hexahydroisoindolo[1,2-*b*]quinazolin-6-ones (7 and 8). General procedure

A mixture of 2-carboxybenzaldehyde (1) (1.5 g, 0.01 mol), *cis*- or *trans*-2-amino-1-cyclohexylmethylamine (**2a**) or (**2b**) (1.3 g, 0.01 mol) or -4-cyclohexenyl-1-methylamine (**2c**) or (**2d**) (1.3 g, 0.01 mol) and *p*-toluenesulphonic acid (0.05 g) in dry chlorobenzene (50 mL) was refluxed for 6 h with use of a water separator. After cooling, the mixture was evaporated to dryness at reduced pressure. For the preparation of **3-5**, the residue was separated by HPLC; eluent: *n*-hexane–MeOH–*i*-PrOH–CH_2Cl_2 (90 + 4 + 1 + 5 v/v%); flow rate: 1 ml/min. For **6-8**, it was transferred to an Al_2O_3 column (basic Al_2O_3, activated, 50-200 μm, Janssen) and eluted with EtOAc. After the solvent was evaporated off, the residues were crystallized. Data on **3-8** are listed in Table 3.

Table 3. Physical and analytical data for compounds (**3-8**)*

Compd	mp °C	Yield %	Formula	Analysis Calcd % C	H	N	Found % C	H	N
3	172-174[a]	24	$C_{15}H_{18}N_2O$	74.35	7.49	11.64	74.27	7.36	11.50
4	177-179[a]	20	$C_{15}H_{18}N_2O$	74.35	7.49	11.64	74.39	7.38	11.71
5	148-150[b]	33	$C_{15}H_{18}N_2O$	74.35	7.49	11.64	74.50	7.61	11.65
6	127-129[b]	62	$C_{15}H_{18}N_2O$	74.35	7.49	11.64	74.81	7.61	11.73
7	167-168[c]	68	$C_{15}H_{16}N_2O$	74.97	6.71	11.66	75.11	6.82	11.79
8	115-117[b]	64	$C_{15}H_{16}N_2O$	74.97	6.71	11.66	75.08	6.67	11.81

*Crystallization solvent: [a]EtOH, [b]EtOAc, [c]dioxan

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REFRENCES

1. G. Stájer, F. Csende, G. Bernáth, and P. Sohár, *Heterocycles*,1994, **37**, 883.
2. A. E. Szabó, G. Stájer, P. Sohár, R. Sillanpää, and G. Bernáth, *Acta Chem. Scand.*, 1995, **49**, 751.
3. S. Silvano, A. Pasini, E. Menta, F. Zunino, and S. Tognella, *PCT Int. Appl. WO* 89 09,218, 1989 (*Chem. Abstr.*, 1991, **114**, 16606k).
4. P. Sohár, *Nuclear Magnetic Resonance Spectroscopy*, CRC Press, Boca Raton, Florida, 1983, (a) Vol. 2, p. 43 and Vol. 3, p. 2-4; (b) Vol. 2, pp. 154, 155; (c) Vol. 1, pp. 196, 197; (d) Vol. 2, pp. 153, 154.
5. D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, 1967, **89**, 5315.
6. J. K. M. Sanders and J. D. Mersch, *Prog. Nucl. Magn. Reson.*, 1982, **15**, 353, and references cited therein.
7. J. Mason, *J. Chem. Soc.*, A, **1971**, 1038.
8. G. Stájer, A. E. Szabó, G. Bernáth, and P. Sohár, *J. Mol. Struct.* accepted for publication.
9. D. T. Pegg, D. M. Doddrell, and M. R. Bendall, *J. Chem. Phys.*, 1982, **77**, 2745.
10. M. R. Bendall, D. M. Doddrell, D. T. Pegg, and W. E. Hull, *High Resolution Multipulse NMR Spectrum Editing and DEPT*, Bruker, Karlsruhe, 1982.
11. R. R. Ernst, G. Bodenhausen, and A. Wokaun, *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Clarendon Press, Oxford, U. K., 1987, pp. 471-479.

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