Short Communication

An Efficient Synthesis of Stereoisomeric 2-(Substituted)-Aminocyclohexanecarboxamides

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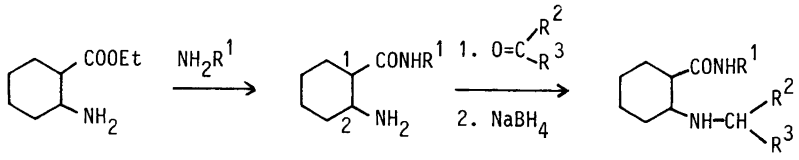
It is well known that many compounds possessing a carboxamide moiety show a variety of pharmacological effects.[1] The 2-aminocycloalkanecarboxamides exert a pronounced tranquilizing effect on the central nervous system.[2–4]

Very recently, a simple and rapid method has been developed for the reductive alkylation of 2- and 3-alkanolamines (**3**) using carbonyl compounds and sodium borohydride.[3,4] The method was readily applicable to the synthesis of stereoisomeric alicyclic 1,3-aminoalcohols.[5] It combines the formation of oxazolidines or oxazines (**2**) from aminoalcohols (**1**) and oxo compounds with facile sodium borohydride reduction of the labile tautomer mixture thus obtained.[6,7]

The above method has now been used to synthesize the title compounds. The latter are not only of pharmacological potential but are also suitable ligands for the synthesis of platinum complexes possessing anticancer activity;[8–10] they are also starting materials for the synthesis of saturated analogues of quinazolinone alkaloids.[11–14]

Results and discussion

Armarego[15,16] reported that *cis*- and *trans*-2-aminocyclohexanecarboxamides (**5a,b**) and *trans*-2-aminocyclohexane-*N*-methylcarboxamide (**6b**) were formed by the reaction between aminoesters (**4a,b**) and methanolic ammonia or methylamine in a sealed tube at 110–120 °C for 20 h. The crude *cis* amide (**6a**) has been prepared from the tosyl derivative of **6a** but no melting



4a,b

cis: **a**
trans: **b**

R^1=H : **5a,b**
R^1=Me: **6a,b**

R^1	R^2	R^3	
H	Me	Me	**7a,b**
Me	Me	Me	**8a,b**
H	$-(CH_2)_5-$		**9a,b**
H	Me	Et	**10b**
H	H	C_6H_4Cl	**11a,b**

Scheme 1.

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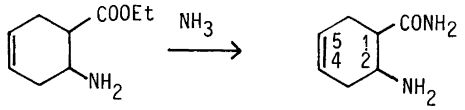
point was reported.[17] We found that the amidation of esters **4a,b** takes place even under very mild conditions, forming products **5a,b** and **6a,b** in good yields. These amides reacted readily with ketones (acetone, cyclohexanone and 2-butanone were used) in ethanol solution. Without isolation of the products, the mixture was treated with sodium borohydride in boiling ethanol and derivatives **7a,b–9a,b** were obtained in good yields. Starting from **5b** and 2-butanone, a mixture of the *threo* and *erythro* isomers of **10b** was formed. The method is also applicable to aldehydes: starting from *p*-chlorobenzaldehyde, compounds **11a,b** were prepared (Scheme 1).

The above, mild amidation procedure was also applied to the preparation of ethyl *cis*-2-amino-4-cyclohexenecarboxylate (**12**)[18] which then gave **13** (Scheme 2).

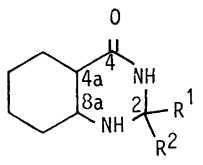


12 **13**

Scheme 2.

It was found also that the reaction of cyclohexanone with **5a,b** is very fast even at room temperature, and a catalytic reductive alkylation method was thus applied to synthesize compounds **9a,b**. In the presence of a platinum catalyst under hydrogen atmosphere and under normal conditions, the *N*-cyclohexyl derivatives **9a,b** were formed in nearly quantitative yields.

In some cases the intermediate products were also isolated (**14a,b** and **15a,b**).



$R^1=R^2$=Me : **14a,b**

R^1,R^2= $-(CH_2)_5-$: **15a,b**

cis: **a** *trans:* **b**

These compounds have stable perhydroquinazolinone structures, and no ring-chain tautomerism as in 1,3-oxazolidines or 1,3-oxazines could be observed. The slightly more vigorous reduction conditions required here than in the reduction of **2** to **3** can be explained by the stability of the perhydroquinazolinone structure. The aromatic analogues were also reductible with sodium borohydride in boiling ethanol.[20]

Experimental

Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra (data in Tables 1 and 2) were recorded at ambient temperature on a JEOL GX-400 FT NMR spectrometer in 5 mm tubes, using $CDCl_3$ as solvent and TMS as internal standard. The IR spectra were recorded on a PE 180 IR spectrometer by the KBr tablet method.

2-Aminocyclohexanecarboxamides (**5a,b–6a,b**). Ethyl *cis*- or *trans*-2-aminocyclohexanecarboxylate[16] (3.42 g, 20 mmol) was dissolved in 50 ml of methanolic ammonia (20 % NH_3) or methanolic methylamine (20 % CH_3NH_2). The solution was kept at room temp. for 3 weeks (NH_3) or 10 d (CH_3NH_2). The solvent was then evaporated and the residue crystallized from ethyl acetate. By repeating the amidation of the mother liquor, more product could be obtained. **5a**: Yield 68 %, m.p. 125–127 °C (from EtOAc; lit.[15] yield 46 %, m.p. 124 °C), IR/C=O 1665 cm^{-1}. **5b**: Yield 64 %, m.p. 155–156 °C (from EtOAc; lit.[15] yield 69 %, m.p. 153–153.5 °C), IR/C=O 1650 cm^{-1}. **6a**: Yield 69 %, m.p. 80–83 °C (from *n*-hexane/acetone), IR/C=O 1645 cm^{-1}; anal. $C_8H_{16}N_2O$: C, H, N. **6b**: Yield 66 %, m.p. 91–93 °C (from *n*-hexane/acetone; lit.[17] yield 57 %, m.p. 90–91.5 °C), IR/C=O 1645 cm^{-1}.

The cyclohexene derivative **13** was prepared in the same way starting from **12**.[19] Yield 66 %, m.p. 126–128 °C (from EtOAc), IR/C=O 1660 cm^{-1}; anal. $C_7H_{12}N_2O$: C, H, N. ^1H NMR: δ 5.75 (H-5), 5.60 (H-4), 3.42 (H-2) ppm; $J_{H\text{-}1,H\text{-}2}$ 2.4 Hz.

2-(Substituted)aminocyclohexanecarboxamides (**7a,b**, **8a,b**, **10b** and **11a,b**). Carboxamide **5** or **6** (2 mmol) was dissolved in 10 ml of ethanol, and the carbonyl compound (3 equiv. of acetone or 2-butanone, 1.5 equiv. of cyclohexanone, 1

Table 1. Selected ^{1}H NMR data for 2-aminocyclohexanecarboxamides **5–11**.

Compound	δ(H-1)/ppm	δ(H-2)/ppm	$J_{H\text{-}1,H\text{-}2}$/Hz	δ(*N*-Substituents)/ppm
5a	1.89	3.30	3.5	–
5b	1.89	2.86	10.1	–
6a	1.80	3.26	3.5	2.78 (CH_3)
6b	1.79	2.90	10.0	2.81 (CH_3)
7a	2.03	3.01	3.6	1.05, 1.10 [$CH(CH_3)_2$]; 2.93 [$CH(CH_3)_2$]
7b	1.93	3.01	10.8	1.01, 1.05 [$CH(CH_3)_2$]; 2.97 [$CH(CH_3)_2$]
8a	1.92	3.01	3.7	1.04, 1.11 [$CH(CH_3)_2$]; 2.91 [$CH(CH_3)_2$] 2.73 (CH_3)
8b	1.88	2.65	11.0	1.01, 1.07 [$CH(CH_3)_2$]; 2.96 [$CH(CH_3)_2$]; 2.78 (CH_3)
9a	2.05	3.06	3.5	2.33 (−NH−CH<)
9b	1.92	2.66	10.8	2.58 (−NH−CH<)
10b[a]	1.95	2.66	10.7	0.89 (CH_2CH_3); 0.99 ($CHCH_3$); 2.74 (−NH−CH<)
10b[b]	1.95	2.63	10.6	0.86 (CH_2CH_3); 1.02 ($CHCH_3$); 2.74 (−NH−CH<)
11a	2.15	2.96	3.5	3.80, 3.75 (CH_2Ph, J = −13.1 Hz)
11b	2.02	2.70	11.1	3.87, 3.68 (CH_2Ph, J = −12.8 Hz)

[a]Major isomer. [b]Minor isomer; isomer ratio 6:4.

equiv. of *p*-chlorobenzaldehyde) was added. The mixture was heated under reflux for 10–13 min (the completion of the reaction was monitored by TLC) and sodium borohydride (0.15 g, 4 mmol) was then added at room temp. over a period of a few min. After stirring for 20 min at room temp. and heating under reflux for 20–40 min, the complex was decomposed with 10 ml of water. After evaporation of the ethanol the product was extracted into chloroform. Products **8a,b**, **10b** and **11a** were oily and for elementary analysis they were transformed to crystalline picrates or hydrochlorides. **7a**: Yield 62 %, m.p. 73–75 °C (from *n*-hexane), IR/C=O 1650 cm^{-1}; anal. $C_{10}H_{20}N_2O$: C, H, N. **7b**: Yield 73 %, m.p. 93–94 °C (from *n*-hexane); IR/C=O 1650 cm^{-1} anal. $C_{10}H_{20}N_2O$: C, H, N. **8a**: Yield 64 %, m.p. 128–130 °C (as picrate from acetone/ether), IR/C=O 1635 cm^{-1}; anal. $C_{17}H_{25}N_2O_8$: C, H, N. **8b**: Yield 68 %, m.p. 145–148 °C (as picrate from acetone/ether), IR/C=O 1630 cm^{-1}; anal. $C_{17}H_{25}N_2O_8$: C, H, N. **10b**: Yield 72 %, m.p. 174–175 °C (as picrate from acetone/ether), IR/C=O 1630 cm^{-1}; anal. $C_{17}H_{25}N_2O_8$: C, H, N. **11a**: Yield 80 %, m.p. 219–222 °C (as hy-

Table 2. Selected ^{1}H and ^{13}C NMR data for perhydroquinazolin-4-ones **14a,b** and **15a,b**.

Compound	δ(H-4a)/ppm	δ(H-8a)/ppm	$J_{H\text{-}4a,H\text{-}8a}$/Hz	$\Sigma J_{H\text{-}8a}$/Hz
14a	2.20	3.36	3.5	10.5
14b	1.65	2.70	11.0	25.3
15a	2.21	3.30	3.5	~11
15b	1.67	2.66	10.8	25.5

Compound	δ(C-2)/ppm	δ(Other C)/ppm
14a	67.9	174.6, 45.5, 41,9, 31.8, 29.8, 29.0, 25.5, 25.1, 25.0
14b	68.1	172.3, 52.3, 48.1, 33.4, 32.0, 29.5, 25.9, 25.5, 25.5
15a	69.1	174.6, 44.8, 42.8, 41.0, 37.2, 29.9, 25.7, 25.2, 25.2, 22.5, 22.1, 20.1
15b	69.2	172.4, 51.5, 48.9, 41.2, 37.8, 33.5, 25.9, 25.5, 25.5, 25.2, 22.4, 22.0

drochloride from ethanol/ether), IR/C=O 1655 cm^{-1}; anal $C_{14}H_{20}Cl_2N_2O$: C, H, N. **11b**: Yield 77%, m.p. 117–118°C (from *n*-hexane), IR/C=O 1660 cm^{-1}; anal. $C_{14}H_{19}ClN_2O$: C, H, N.

*2-Cyclohexylaminocyclohexanecarboxamides (**9a,b**).* Platinum oxide (30 mg) was pre-hydrogenated in 10 ml of ethanol, and carboxamide **5a** or **5b** (0.14 g, 1 mmol) and cyclohexanone (0.2 g, 2 mmol) were added. The mixture was stirred under hydrogen atmosphere and under normal conditions. On completion of the reduction (1.5 h, monitored by TLC) the catalyst was filtered off, the solvent and the excess cyclohexanone were evaporated and the products were recrystallized from *n*-hexane and *n*-hexane/acetone, respectively. **9a**: Yield 86%, m.p. 123–124°C, IR/C=O 1655 cm^{-1}; anal. $C_{13}H_{24}N_2O$: C, H, N. **9b**: Yield 87%, m.p. 81–83°C, IR/C=O 1650 cm^{-1}; anal. $C_{13}H_{24}N_2O$: C, H, N.

*Quinazolinone intermediates (**14a,b–15a,b**). Carboxamide* **5a** or **5b** (0.14 g, 1 mmol) was heated under reflux in 10 ml of ethanol with acetone (3 mmol) or cyclohexanone (1.5 mmol) for 30 or 15 min, respectively. After evaporation of the solvent, **14a,b** or **15a,b** was obtained as a white crystalline solid. All four compounds were recrystallized from *n*-hexane. **14a**: Yield 89%, m.p. 143–145°C, IR/C=O 1665 cm^{-1}; anal. $C_{10}H_{18}N_2O$: C, H, N. **14b**: Yield 64%, m.p. 164–165°C, IR/C=O 1645 cm^{-1}; anal. $C_{10}H_{18}N_2O$: C, H, N. **15a**: Yield 69%, m.p. 148–149°C, IR/C=O 1660 cm^{-1}; anal. $C_{13}H_{22}N_2O$: C, H, N. **15b**: Yield 66%, m.p. 190–191°C, IR/C=O 1645 cm^{-1}; anal. $C_{13}H_{22}N_2O$: C, H, N.

The sodium borohydride reduction (as described above) of quinazolinones **14a,b** and **15a,b** resulted in compounds **8a,b** and **9a,b**.

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