INVESTIGATIONS ON ISOQUINOLINES

Preparation of Carboxamides with Potential Pharmacological Activity, III* Synthesis of 6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetamides

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The preparation of fifteen 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetamides is described. The mixed anhydride of 2-carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetic acid with isobutyl chloroformate was reacted with the corresponding amines at -10 to -15 °C. The carbobenzyloxy protecting group was removed from the 2-carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetamides by means of HBr in acetic acid.

In the course of our work aiming at the preparation of carboxamides with pharmacological activity, we earlier synthesized numerous *N*-acyl aminomethylcyclopentane and cyclohexane derivatives [1—3]. Similarly to related derivatives [4], these compounds proved to act on the central nervous system. Among the alicyclic β-amino carboxamides prepared subsequently [5, 6], numerous compounds proved to exert antypiretic, analgetic or narcosis enhancing effects. This circumstance prompted us to synthesize for pharmacological purposes some related carboxamide derivatives of 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetic acid, a β-amino acid used also in our earlier investigations [7].

With the aim of preparing tranquilizing and hypotensive azabenzopyridocolines and related compounds, LOMBARDINO *et al.* synthesized some 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetamides (**6**) [8, 9]. They obtained the isoquinolineacetamides from 1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**1**) by refluxing under nitrogen protecting blanket with a high excess of the corresponding amine for 24 hrs. However, the yield, *e.g.* in the case of the 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinoline-*N*-*n*-butylacetamide, was only 50%. Though the yields reached with amines of higher boiling points were somewhat higher and also a recent application of the method is known [10], it seemed desirable to attempt the application of another way of synthesis.

* Part II: G. Bernáth, L. Gera, Gy. Göndös, I. Pánovics, Z. Ecsery: Acta Chim. (Budapest) **89**, 61 (1976).

Table I

α-[1-(2-Carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]-acetamides (**5a – o**)

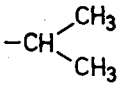
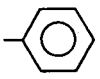
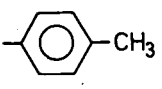
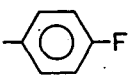
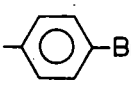
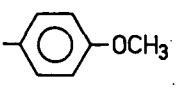
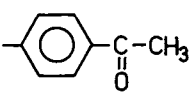
No.	R	Formula, Molecular weight	M.p. (°C); Solvent of crystallization	Analysis (%) Calcd./Found C	H	N
5a		$C_{24}H_{30}N_2O_5$ 426.50	158—160 Benzene—ether	67.58 67.83	7.09 7.23	6.57 6.28
5b		$C_{27}H_{34}N_2O_5$ 466.56	164—166 Benzene	69.50 69.15	7.35 7.24	6.01 6.25
5c		$C_{27}H_{28}N_2O_5$ 460.51	104—106 Benzene—ether	70.41 69.91	6.13 6.05	6.08 6.17
5d		$C_{28}H_{30}N_2O_5$ 474.54	168—169 Ethanol	70.86 70.81	6.37 6.41	5.90 6.16
5e		$C_{27}H_{27}FN_2O_5$ 478.50	142—144 Benzene—ether	67.77 67.47	5.69 5.75	5.86 6.00
5f		$C_{27}H_{27}BrN_2O_5$ 539.41	152—154 Ethanol—ether	60.11 59.86	5.04 5.00	5.19 5.09
5g		$C_{28}H_{30}N_2O_6$ 490.54	145 Benzene—petroleum ether	68.55 68.87	6.16 6.55	5.71 5.85
5h		$C_{29}H_{30}N_2O_6$ 502.55	185—186 Benzene	69.30 69.64	6.02 6.63	5.58 6.02

Table I (Continued)

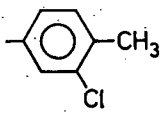
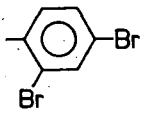
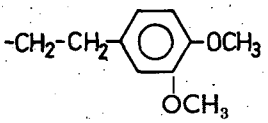
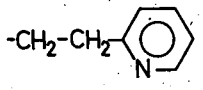
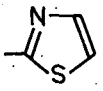
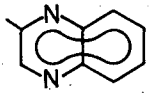
No.	R	Formula, Molecular weight	M.p. (°C); Solvent of crystallization	Analysis (%) Calcd./Found C	H	N
5i		$C_{28}H_{29}ClN_2O_5$ 508.99	125—126 Benzene—ether	66.07 66.40	5.74 6.01	5.51 5.74
5j		$C_{27}H_{26}Br_2N_2O_5$ 618.33	168—169 Benzene	52.44 52.55	4.24 4.46	4.53 4.41
5k		$C_{31}H_{36}N_2O_7$ 548.61	132—134 Benzene—ether	67.86 68.02	6.61 6.55	5.10 5.85
5l		$C_{26}H_{27}N_3O_5$ 461.50	113—115 Benzene—ether	67.66 67.32	5.90 6.15	9.11 8.92
5m		$C_{28}H_{31}N_3O_5$ 489.56	119—121 Benzene—ether	68.69 68.85	6.38 6.46	8.58 8.46
5n		$C_{24}H_{25}N_3O_5S$ 467.47	Oil	61.66 62.02	5.39 5.56	8.99 8.75
5o		$C_{29}H_{27}N_4O_5$ 512.55	166—167 Ethanol—ether	67.91 67.89	5.50 5.95	10.93 10.85

Table II

α-[1-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]-acetamides **(6a – o)**

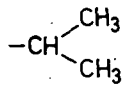
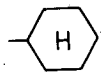
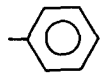
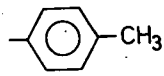
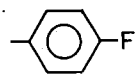
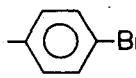
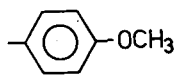
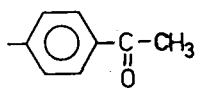
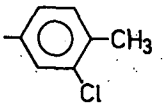
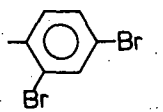
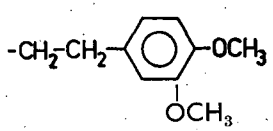
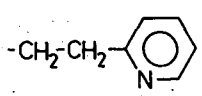
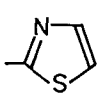
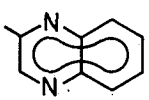
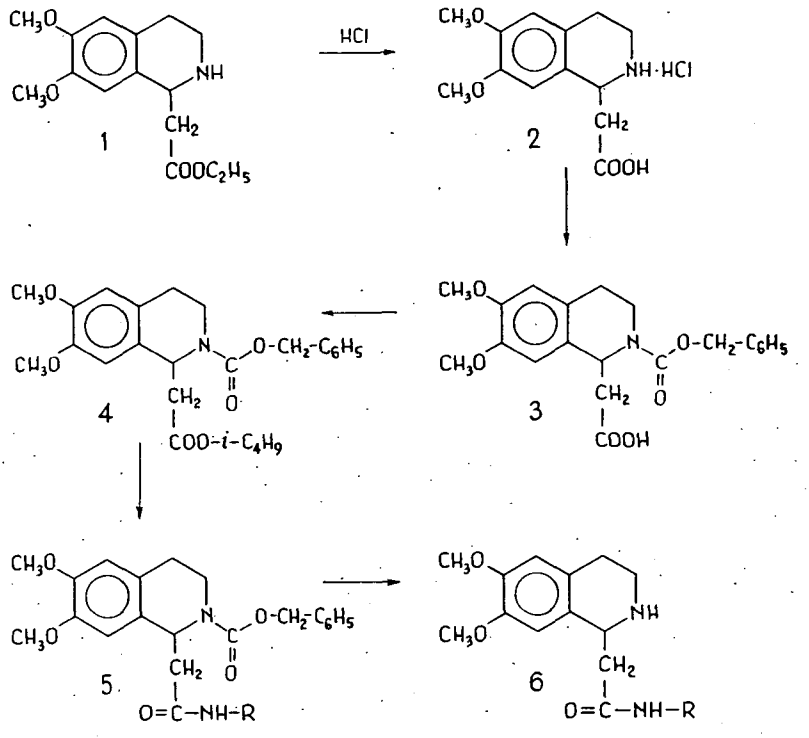
No.	R	Formula, Molecular weight	M.p. (°C); Solvent of crystallization	Analysis (%) Calcd./Found C	H	N	Br	Note
6a		$C_{16}H_{25}BrN_2O_3$ 273.29	192—193 Ethanol—water 4:1	51.47 50.94	6.75 6.91	7.50 7.60	21.40 21.62	a)
6b		$C_{19}H_{29}BrN_2O_3$ 413.36	184—186 Ethanol	55.20 55.23	7.07 7.20	6.78 6.71	19.33 18.99	a)
6c		$C_{19}H_{23}BrN_2O_3$ 407.31	232—233 Ethanol—water 3:2	56.02 55.92	5.69 5.67	6.88 6.49		
6d		$C_{20}H_{25}BrN_2O_3$ 421.34	253—254 Ethanol—water 3:2	57.01 57.25	5.98 6.10		18.97 18.67	a)
6e		$C_{19}H_{22}BFrN_2O_3$ 425.30	232—234 Ethanol—water 4:1	53.65 54.02	5.21 5.35	6.59 6.14	18.19 18.18	a)
6f		$C_{19}H_{22}BrN_2O_3$ 486.22	234—236 Ethanol—water 3:2	46.93 46.80	4.56 4.50		32.87 32.90	b)
6g		$C_{20}H_{25}BrN_2O_4$ 437.33	238—239 Ethanol—water 2:3	54.92 55.12	5.76 5.69	6.40 6.63		
6h		$C_{21}H_{25}BrN_2O_4$ 449.35	206—208 Ethanol—water 7:3	56.13 55.98	5.61 5.85	6.24 6.17		

Table II (Continued)

No.	R	Formula, Molecular weight	M.p. (°C); Solvent of crystallization	Analysis (%) Calcd./Found C	H	N	Br	Note
6i		$C_{20}H_{24}BrClN_2O_3$ 455.79	224—225 Ethanol—water 4:1	52.70 53.01	5.31 5.48	6.15 6.11	17.53 17.40	a)
6j		$C_{19}H_{21}Br_3N_2O_3$ 565.13	207—208 Ethanol—water 9:1	40.38 40.79	3.75 3.93	4.96 4.91	14.13 14.57	a)
6k		$C_{23}H_{31}ClN_2O_5$ 450.95	194—195 Ethanol—ether	61.26 61.10	6.93 6.78	6.21 6.39		c)
6l		$C_{18}H_{23}Br_2N_3O_3 \cdot H_2O$ 507.24	224—226 Ethanol—water 9:1	42.61 42.36	4.96 5.12	8.28 8.66	31.51 30.98	e)
6m		$C_{20}H_{25}N_3O_3$ 355.43	104 Benzene—ether	67.58 68.02	7.09 7.17		11.82 11.99	d)
6n		$C_{16}H_{20}BrN_3O_3S$ 414.27	238—240 Ethanol—water 1:1	46.39 46.53	4.87 5.03		19.29 19.12	a)
6o		$C_{21}H_{23}BrN_4O_3 \cdot H_2O$ 477.36	192—194 Ethanol—water 7:3	52.83 52.83	5.28 5.23	11.74 11.38	16.76 16.48	e)

Note: a) Ionic bromide.
b) Ionic+covalent bromide.
c) Hydrochloride. Cl^- Calcd.: 7.86%. Found: 7.90%. Base: $C_{23}H_{30}N_2O_5$ (414.49). Calcd.: C 66.64; H 7.29; N 6.76. Found: C 66.70; H 7.56; N 6.86%.
d) Base.
e) Analysis for this compound with one mole crystal water is satisfactory.



The mixed anhydride method [11] used in peptide chemistry appeared suitable for this purpose. The secondary amino group of the 1-carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**) obtained by HCl hydrolysis of 1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1**) was protected by benzyl chloroformate. The mixed anhydride of 2-carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetic acid with isobutyl chloroformate (**4**), formed in THF solution in the presence of triethylamine, was reacted with the corresponding amines at −10 to −15 °C. The carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetamides (**5a—o**) (Table I) were obtained with a very good yield (about 80—90%). The carbobenzyloxy protecting group was removed by HBr in acetic acid.

It has to be mentioned, that the use of the *p*-toluenesulfonyl protecting group in preparing the amides of related *β*-amino acids is also found. In a recent paper [12] ARMAREGO pointed out that the reaction of *cis*-hexahydroantranilic acid with alcoholic methyl amine or ammonia solution being slow, he prepared the desired amides from acid chlorides using *p*-toluenesulfonyl protecting group. Removal of the *p*-toluenesulfonyl protecting group is, however, possible only by sodium in liquid ammonia. Protection of the amino acid by benzyloxycarbonyl group proved not suitable because debenzylation occurred during the preparation of the acid

chloride. The method described in our paper is similar to that found suitable also by ARMAREGO.

The results of pharmacological testing of the 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetamides (**6a—o**) prepared will be dealt with elsewhere.

Experimental

2-Carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetic acid (**3**)

28.7 g (0.1 mole) 6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinoline acetic acid hydrochloride (**2**) was solved under stirring in 50 ml aqueous solution of 4 g sodium hydroxide, and 17 g (0.1 mole) benzyl chloroformate was added dropwise in 30 minutes under cooling. Then the cooled reaction mixture was stirred for further 3 hrs and acidified with 40 ml 20% HCl solution. The white crystals obtained were recrystallized from benzene—ether mixture. M.p. 153—154 °C, yield 32.5 g (84.4%).

$C_{21}H_{23}O_6N$ (385.40). Calcd. C 65.44; H 6.01; N 3.63. Found C 65.26; H 5.90; N 3.46%.

2-Carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinoline acetamides (**5a—o**)

0.02 mole 2-Carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinoline-acetic acid (**3**) solved in 80 ml abs. tetrahydrofurane was cooled in an ice—salt cooling mixture to −10 to −15 °C, then 5 ml each of the tetrahydrofurane solutions of 0.02 mole triethylamine and 0.02 mole isobutyl chloroformate were added simultaneously in 5 minutes under intensive stirring. After further 5 minutes stirring 0.02 mole of the corresponding amine solved in 20 ml tetrahydrofurane was added dropwise to the reaction mixture, stirred for further 5 hrs and left to stand overnight. The triethylamine hydrochloride precipitated was filtered, washed twice with 5 ml tetrahydrofurane, then the combined tetrahydrofurane solution was evaporated in vacuum. The residue was dissolved in 70 ml ethyl acetate, washed with 2×6 ml water and with 1% sodium hydroxide solution, finally washed to neutrality with 4×5 ml water. After drying over sodium sulfate, the ethyl acetate was evaporated in vacuum and the residue was crystallized. The data of the products obtained (**5a—o**) are summarized in Table I.

6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetamides (**6a—o**)

To 0.015 mole 2-carbobenzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinoline acetamides (**5a—o**) 4 to 5 equivalents of a 30% HBr solution in glacial acetic acide was added. Shaking the mixture, a homogeneous solution was obtained which solidified after 30 to 50 minutes. The precipitation of the carboxamide hydrobromide was completed by adding ether. The crystalline product obtained was washed thoroughly with ether, then with acetic acid and recrystallized after drying. The compounds synthesized (**6a—o**) are listed in Table II.

References

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[2] *Bernáth, G., K. Kovács, E. Pálosi, P. Görög, L. Szporny:* Hung. Pat. 156.542, 25. Apr., 1969.
[3] *Bernáth, G., K. Kovács, E. Pálosi, P. Görög, L. Szporny:* Austrian Pat. 286.959, 11 Jan., 1971.
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ИССЛЕДОВАНИЕ ПРОИЗВОДНЫХ ИЗОХИНОЛИНА, III. СИНТЕЗ ПОТЕНЦИАЛЬНЫХ ФАРМАКОНОВ АМИДНОГО ХАРАКТЕРА. СИНТЕЗ 6,7-ДИМЕТОКСИ-1,2,3,4-ТЕТРАГИДРО-1-ИЗОХИНОЛИНАЦЕТАМИДОВ

Е. Кобор и Г. Бернат

Сообщается о синтезе производного 6,7-диметокси-1,2,3,4-тетрагидро-1-изохинолинацетамида. Из 2-карбобензилокси-6,7-диметокси-1,2,3,4-тетрагидро-1-изохинолинуксусной кислоты и изобутил-хлорформата образовавшийся смешанный аигидрид был введен в реакцию с соответствующими аминами при температурах −10 и −15 °С. Из полученных 2-карбобензилокси-6,7-диметокси-1,2,3,4-тетрагидро-1-изохинолинацетамидов защитную карбобензилоксидную группу удаляли с помощью бромистого водорода в среде ледяной уксусной кислоты.