Chemistry of Heterocyclic Compounds, Vol. 48, No. 5, August, 2012 (Russian Original Vol. 48, No. 5, May, 2012)

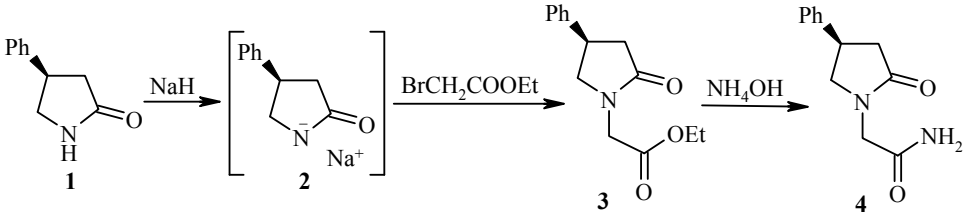
NOVEL METHODS FOR THE SYNTHESIS OF 2-[(4*R*)-2-OXO-4-PHENYLPYRROLIDIN-1-YL]-ACETAMIDE ((*R*)-PHENOTROPIL)

M. Vorona[1], G. Veinberg[1]*, S. Vikainis[1], E. Kuznetsov[1], A. Lebedev[1], Yu. Ponomarev, A. Chernobrovijs[1], L. Zvejniece[1] and M. Dambrova[1]

Two novel methods have been developed for the preparation of 2-[(4R)-2-oxo-4-phenylpyrrolidin-1-yl]acetamide ((R)-Phenotropil). In the first, n-butyl (3R)-4-amino-3-phenylbutyrate is alkylated with haloacetamide in DMF in the presence of potassium phosphate monohydrate, and the intermediate 4-carbamoylmethylamino-3-phenylbutyrate is subsequently cyclized by refluxing in toluene in the presence of potassium phosphate monohydrate and tetrabutylammonium bromide. In the second, chloroacetonitrile is used under similar conditions in place of the haloacetamide. Both methods lead to (R)-Phenotropil in 40-60% yields calculated on the starting n-butyl (3R)-4-amino-3-phenylbutyrate .

Keywords: *n*-butyl (3*R*)-4-carbamoylmethylamino-3-phenylbutyrate, *n*-butyl (3*R*)-4-cyanomethyl-amino-3-phenylbutyrate, 2-[(4*R*)-2-oxo-4-phenylpyrrolidin-1-yl]acetamide, alkylation, cyclization.

Phenotropil (2-[(4*R*)-2-oxo-4-phenylpyrrolidin-1-yl]acetamide) is a member of the racetam group of nootropic drugs, which contain a 2-pyrrolidone ring [1]. The presence of a chiral center at the position 4 of the Phenotropil molecule leads to its possible medicinal use both as a racemic mixture and also in an enantiomeric form. Until 2006, there were no data in the literature on methods of synthesis and the activity of the (*R*)- and (*S*)-enantiomers of Phenotropil. Our method for the preparation of the stereoisomers and a comparative study of their pharmacological properties revealed the marked predominance of antidepressant activity in the (*R*)-Phenotropil, when compared to its (*S*)-antipode. It was also shown that an identical effect on muscle tone and movement coordination in mice is achieved with a lower dose of the (*R*)-Phenotropil, compared to its (*S*)-isomer [2].



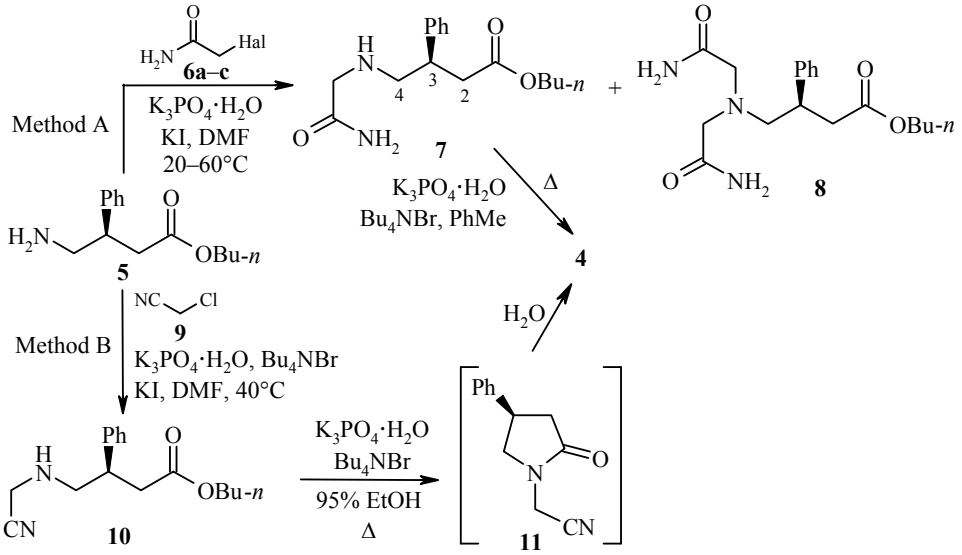
*To whom correspondence should be addressed, e-mail: veinberg@osi.lv.

[1]Latvian Institute of Organic Chemistry, 21 Aizkraukles St., Riga LV-1006, Latvia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 775-778, May, 2012. Original article submitted May 10, 2011.

Our previously reported route of the (*R*)-Phenotropil **4** synthesis [2] was based on known methods [3, 4]. The action of sodium hydride on (4*R*)-4-phenyl-2-pyrrolidone (**1**) gave the sodium derivative **2**, which could then, without isolation, be alkylated by ethyl bromoacetate. The obtained ester **3** was subjected to ammonolysis with aqueous ammonia, to yield the target product **4**.

With the ability of *N*-alkylated 4-aminobutyrates to cyclize to *N*-alkylpyrrolidin-2-ones [5] we considered the possible synthesis of *n*-butyl (3*R*)-4-carbamoylmethylamino-3-phenylbutyrate (**7**) and its cyclization to the target product **4** (method A).



6 a Hal = Cl, **b** Hal = Br, **c** Hal = I

The (*R*)-enantiomer of the *n*-butyl 4-amino-3-phenylbutyrate (**5**) can be prepared by our previously reported biocatalytic method for separating the racemic ester **5** using α-chymotrypsin [6]. The starting material for the synthesis of ester **5** is 4-amino-3-phenylbutyric acid, also known as the tranquilizing agent Phenibut.

Investigation of the proposed method has shown that the base plays a decisive role in the process of *N*-alkylation of ester **5**. With the use of sodium hydroxide, potassium hydroxide, triethylamine, morpholine, or *N*-methylmorpholine, compound **5** predominantly cyclizes to (4*R*)-4-phenyl-2-pyrrolidone (**1**), and this is accompanied by cleavage of *n*-butanol. However, the use of potassium phosphate monohydrate in a polar solvent (DMF) at room temperature or heating at 60ºC gave principally the *N*-alkylated product **7**. The yield was increased with the use of chloroacetamide (**6a**) and a catalytic amount of potassium iodide. Excess bromo- (**6b**) or iodoacetamide (**6c**) promoted formation of the *N*,*N*-bisalkylated product **8**. Cyclization of the *n*-butyl (3*R*)-4-carbamoylmethylamino-3-phenylbutyrate (**7**) to the target 2-[(4*R*)-2-oxo-4-phenylpyrrolidin-1-yl]-acetamide (**4**) took place virtually quantitatively in toluene, when refluxed in the presence of a mixture of potassium phosphate monohydrate and tetrabutylammonium bromide (TLC data).

The optimization of method A included the removal of inorganic salts from the reaction mixture by filtration, substitution of DMF for toluene, addition of potassium phosphate monohydrate and tetrabutylammonium bromide to the obtained solution, and refluxing the mixture for 2 h. This excluded the stage of separation and purification of the monoalkylated intermediate product **7**. Purification of the obtained (*R*)-Phenotropil from pyrrolidone **1**, the *N*,*N*-bis-alkylation product **8** and other impurities was carried out by column chromatography or by recrystallization from water, and the final product was obtained in 63% and 48% yields, respectively (calculated on the starting ester **5**).

The method B is based on a reaction of *n*-butyl 4-amino-3-phenylbutyrate (**5**) and chloroacetonitrile (**9**). The reaction conditions were the same as those mentioned above for the reaction with the acetamides **6a-c**. Short heating of the *n*-butyl (3*R*)-4-cyanomethylamino-3-phenylbutyrate (**10**) in 95% ethanol in the presence of a base led to cyclization and hydrolysis of the cyano group to give the (*R*)-Phenotropil **4** in a 44% yield, based on the starting ester **5**.

The methods developed for the preparation of (*R*)-Phenotropil are not inferior in efficiency to those reported in the literature [2, 3]. Based on the use of *n*-butyl (3*R*)-4-amino-3-phenylbutyrate hydrochloride they extend the material and methodological basis for the preparation of not just this product, but also similarly structured racetams.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury-400 (400 MHz) instrument using $CDCl_3$ with HMDS (δ 0.05 ppm) as internal standard. Elemental analysis was carried out on a Carlo Erba 1108 analyzer. Monitoring of the reaction course was carried out by TLC on Merck Kieselgel plates and visualized with UV light. Chiral HPLC was performed on a Waters Alliance instrument on a Chiralpac IC column (4.6×250 mm) from Daicel, filled with tris-(3,5-dichlorophenylcarbamoyl)cellulose immobilized on silica gel (5 microns). The eluent was ethanol–hexane–ethanolamine (35:65:0.1%), the flow rate was 1 ml/min, and the spectrophotometric detection was done at λ=210 nm. Preparative column chromatography was performed on Merck Kieselgel (0.06-0.20 mm) grade silica gel with CH_2Cl_2–MeOH eluent (10:1, for compound **4**) or CH_2Cl_2–ethanol (15:1, for the remaining compounds). The reagents and materials used in the experiments were from Acros.

***n*-Butyl (3*R*)-4-Carbamoylmethylamino-3-phenylbutyrate (7)**. $K_3PO_4 \cdot H_2O$ (0.691 g, 3 mmol) and 4 Å molecular sieves (2 g) were added to a solution of the *n*-butyl (3*R*)-4-amino-3-phenylbutyrate hydrochloride (**5**) (0.272 g, 1 mmol) and bromoacetamide (**6b**) (0.137 g, 1 mmol) in DMF (20 ml). The suspension was stirred at room temperature for 48 h, filtered, and the filtrate was evaporated *in vacuo*. Compound **7** was isolated by column chromatography. Yield 0.155 g (53%). Oily product, R_f 0.52. The use of a mixture of chloroacetamide (**6a**) (0.094 g, 1 mmol) and KI (0.008 g, 0.05 mmol) in place of bromoacetamide (**6b**) gave a 0.193 g (66%) yield of the ester **7**. With the use of the iodoacetamide (**6c**) (0.185 g, 1 mmol) in place of bromoacetamide (**6b**) the yield of ester **7** was 0.181 g (62%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.88 (3H, t, J = 7.5, $CH_2CH_2CH_2C\underline{H}_3$); 1.17-1.39 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 1.43-1.63 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 2.63 (1H, d, J = 3.8) and 2.67 (1H, d, J = 3.8, 2-CH_2); 2.84 (2H, d, J = 7.5, 4-CH_2); 3.20 (2H, d, J = 4.2, $COC\underline{H}_2NH$); 3.22-3.37 (1H, m, 3-CH); 4.01 (2H, t, J = 7.5, $C\underline{H}_2CH_2CH_2CH_3$); 5.54 (1H, br. s) and 6.23 (1H, br. s, $CONH_2$); 6.89 (1H, br. s, NH); 7.13-7.41 (5H, m, H Ph). Found, %: C 65.86; H 8.37; N 9.67. $C_{16}H_{24}N_2O_3$. Calculated, %: C 65.73; H 8.27; N 9.58.

***n*-Butyl (3*R*)-4,4-Bis(carbamoylmethyl)amino-3-phenylbutyrate (8)**. $K_3PO_4 \cdot H_2O$ (2.36 g, 10.26 mmol), 4Å molecular sieves (3 g), and Bu_4NBr (0.011 g, 0.036 mmol) were added to a solution of *n*-butyl (3*R*)-4-amino-3-phenylbutyrate hydrochloride (**5**) (1.00 g, 3.42 mmol) and iodoacetamide (**6c**) (2.04 g, 11.00 mmol) in DMF (50 ml). The suspension was stirred at 40ºC for 48 h, filtered, and the filtrate was evaporated *in vacuo*. Compound **8** was isolated by column chromatography. Yield 0.55 g (46%). Using bromoacetamide (**6b**) (1.52 g, 11 mmol) in place of iodoacetamide (**6c**) gave 0.51 g (43%) compound **8**. Amorphous substance, R_f 0.20. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, J = 7.2, $CH_2CH_2CH_2C\underline{H}_3$); 1.16-1.37 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 1.42-1.59 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 2.61-2.92 (4H, m, 2,4-CH_2); 3.19 (4H, s, $N(CH_2)_2$); 3.24-3.42 (1H, m, 3-CH); 4.01 (2H, t, J = 6.5, $C\underline{H}_2CH_2CH_2CH_3$); 5.77 (2H, br. s, $CONH_2$); 6.24 (1H, br. s) and 6.89 (1H, br. s, $CONH_2$); 7.16-7.39 (5H, m, H Ph). Found, %: C 61.98; H 7.84; N 12.13. $C_{18}H_{27}N_3O_4$. Calculated, %: C 61.87; H 7.79; N 12.03.

***n*-Butyl (3*R*)-4-Cyanomethylamino-3-phenylbutyrate (10).** $K_3PO_4 \cdot H_2O$ (3.4 g, 14.72 mmol), KI (0.123 g, 0.74 mmol), 4Å molecular sieves (3 g), and Bu_4NBr (0.024 g, 0.074 mmol) were added to a solution

of the *n*-butyl (3*R*)-4-amino-3-phenylbutyrate hydrochloride (**5**) (2.0 g, 7.36 mmol) and chloroacetonitrile (0.7 ml, 11.04 mmol) in DMF (60 ml). The suspension was stirred at 40ºC for 48 h, filtered, and the filtrate was evaporated *in vacuo*. Compound **10** was isolated by column chromatography. Yield 0.95 g (47%). Oily product, R_f 0.64. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.5, $CH_2CH_2CH_2C\underline{H}_3$); 1.38-1.66 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 1.42-1.60 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 1.99 (1H, br. s, NH); 2.53-3.11 (4H, m, 2,4-CH_2); 3.26-3.43 (1H, m, 3-CH); 3.55 (2H, d, *J* = 1.4, $C\underline{H}_2NH$); 4.00 (2H, t, *J* = 7.5, $C\underline{H}_2CH_2CH_2CH_3$); 7.15-7.46 (5H, m, H Ph). Found, %: C 70.16; H 8.21; N 10.33. $C_{16}H_{22}N_2O_2$. Calculated , %: C 70.04; H 8.08; N 10.21.

2-[(4*R*)-2-Oxo-4-phenylpyrrolidin-1-yl]acetamide (4). A. $K_3PO_4 \cdot H_2O$ (19.07 g, 82.8 mmol) and 4Å molecular sieves (10 g) were added to a solution of the *n*-butyl (3*R*)-4-amino-3-phenylbutyrate hydrochloride (**5**) (7.50 g, 27.6 mmol) and iodoacetamide (**6c**) (5.61 g, 30.3 mmol) in DMF (150 ml). The suspension was stirred at 60ºC for 14 h, filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in toluene (150 ml) and $K_3PO_4 \cdot H_2O$ (2 g, 8.68 mmol) and Bu_4NBr (0.05 g, 0.15 mmol) were added to the solution. The suspension was refluxed for 2 h, cooled, filtered, and the filtrate was evaporated to dryness. The final product **4** was purified from impurities by column chromatography. Yield 3.55 g (63%). In a variant of the synthesis using the same amounts of starting materials, the final product was purified by recrystallization from water (35 ml). Yield 2.70 g (48%).

B. $K_3PO_4 \cdot H_2O$ (0.550 g, 2.40 mmol) and Bu_4NBr (0.050 g, 0.15 mmol) were added to a solution of the ester **10** (0.549 g, 2.00 mmol) in 95% ethanol (40 ml). The suspension was refluxed for 2 h, cooled, filtered, and the filtrate was evaporated to dryness. The target product **4** was isolated by column chromatography. Yield 0.192 g (44%); mp 110-112ºC (mp 110ºC [2]; for the racemic product mp 129-130ºC [3]). R_f 0.40. $[\alpha]_D^{20}$ +8.5º (*c* 3.0, MeOH), optical purity 97%. The ^{1}H NMR spectrum of the obtained compound **4** agreed with that given in the literature [2].

This work was carried out within the scope of the European Regional Development Fund (ERDF) (project 2DP/2.1.1.1.0/10/APIA/VIAA/059).

REFERENCES

1. A. G. Malykh and M. R. Sadaie, *Drugs*, **70**, 287 (2010).
2. G. Veinberg, M. Vorona, M. Dambrova, L. Karina, L. Zvejniece, A. Chernobrovijs, and I. Kalvinsh, Latv. Pat. Appl. 13630; *Chem. Abstr.*, **147**, 365386 (2006).
3. O. M. Glozman, I. S. Morozov, L. A. Zhmurenko, and V. A. Zagorevskii, *Khim.-Farm. Zh.*, **14**, No. 11, 43 (1980).
4. A. G. Shipov, E. P. Kramarova, V. V. Negrebetskii, S. A. Pogozhikh, V. I. Akhapkina, and Yu. A. Baukov, *Vestn. RSMU*, **48**, 58 (2006).
5. J. Gobert, C. Giurgea, J.-P. Geerts, and G. Bodson, EP Pat. Appl. 165919; *Chem. Abstr.*, **105**, 97305 (1986).
6. G. Veinberg, M. Vorona, A. Lebedevs, A. Chernobrovijs, and I. Kalvinsh, Latv. Pat. Appl. 13635; *Chem. Abstr.*, **147**, 385825 (2006).