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Synthesis of 2-Phenyl-3-oxa-5-azatricyclo[4.4.0.0^{2,7}]decan-4-one

R. N. Zolotarev and V. V. Razin

St. Petersburg State University, Universitetskii pr. 26, St. Petersburg, 198904 Russia

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Abstract—Cleavage of the lactone ring in 7-phenylbicyclo[3.1.1]heptan-6,7-carbolactone by the action of ammonia and hydrazine and subsequent oxidative cyclization of the resulting hydroxy amide and hydroxy hydrazide gave a cyclic carbamate, 3-oxa-5-azatricyclo[4.4.0.0^{2,7}]decan-4-one.

We previously showed [1] that the relatively accessible tricyclo[4.1.0.0^{2,7}]heptane system can be transformed into less accessible carbo- and heterocyclic systems having a tricyclo[4.*n*.0.0]alkane skeleton via replacement of the central bond in the bicyclobutane fragment by bridging groups of various sizes. In the framework of studies in this line, in the present work we have synthesized cyclic carbamate **I** with a 3-aza-5-oxatricyclo[4.4.0.0^{2,7}]decane skeleton.

As starting compound we used 7-phenylbicyclo-[3.1.1]heptane-6,7-carbolactone (**II**) which was synthesized by us previously [2] from 7-phenyltricyclo-[4.1.0.0^{2,7}]heptane-1-carboxylic acid. Lactone **II** was converted into hydroxy amide **III** by the action of alcoholic ammonia, and the reaction of **II** with anhydrous hydrazine afforded hydroxy hydrazide **IV** (Scheme 1). In both cases, opening of the lactone ring in **II** occurred with complete retention of the initial norpinane configuration. The structure of compounds **III** and **IV** was convincingly proved by the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) which were compared with those of model compounds [3, 4]. In particular, the configuration at C^6 follows from the character of the 6-H signal which appears in the ^{1}H NMR spectrum as a singlet. The configuration at C^7 was deduced from the position of the 3-H signals which are displaced upfield due to shielding by the *syn*-oriented phenyl substituent on C^7. The target cyclic carbamate **I** was obtained by oxidative cyclization of hydroxy amide **III** by the action of lead tetraacetate [5], as well as by treatment of hydrazide **IV** with nitrous acid [6] (Scheme 1).

On the basis of general considerations [7], we presume that compounds **III** and **IV** are converted into cyclic carbamate **I** through the same intermediate, hydroxy isocyanate **V**. The structure of **I** was confirmed by the ^{1}H and ^{13}C NMR spectra (Tables 1, 2). As might be expected, the spectral parameters of the norpinane fragments in compounds **I**, **III**, and **IV** differ mainly by the chemical shifts and multiplicities of the 6-H signal and the chemical shifts of C^6 and especially C^7.

To conclude, it should be noted that the proposed relatively simple procedure for the synthesis of carbamate **I**, which can be regarded as a protected 1,3-aminoalcohol, opens new prospects in the preparation of functionally substituted norpinane derivatives, including hetero analogs.

Scheme 1.

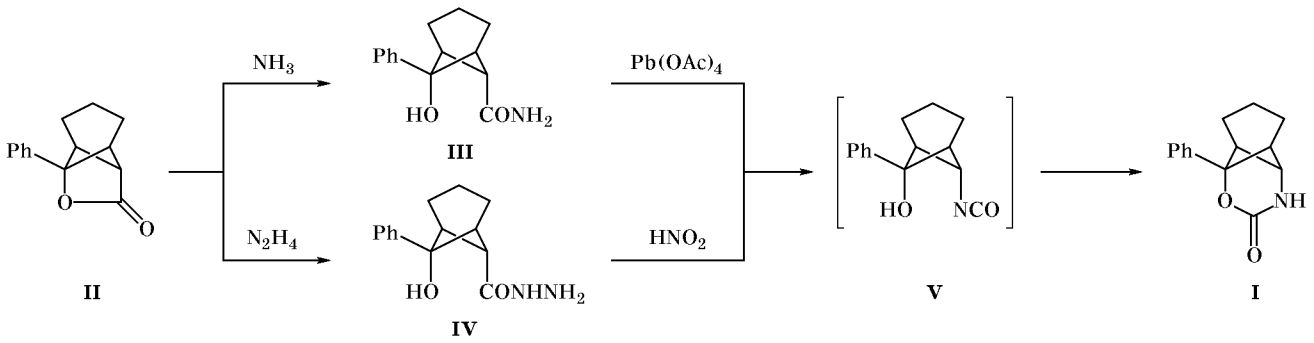

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Table 1. ^{1}H NMR spectra of compounds **I**, **III**, and **IV**, δ, ppm (*J*, Hz)[a]

Comp. no.	3-H	2-H, 4-H	1-H, 5-H	6-H	Other signals
I[b]	0.93–1.10 1.26–1.43	1.95–2.15	2.74 br.s	3.51 d [5.1]	7.23–7.33 and 7.35–7.49 (2H + 3H, Ph), 7.63 s (NH)
III	0.65–0.87 1.18–1.37	1.87–2.13	2.87 br.s	2.31 s	6.57 br.s (OH), 6.65 br.s (1H, NH), 7.10–7.33 (6H, Ph and NH)
IV	0.62–0.86 1.14–1.35	1.82–2.15	2.86 br.s	2.26 s	3.30–5.90 (3H, NH_2 and OH), 7.04–7.35 (Ph), 9.06 br.s (NH)

[a] The spectrum of compound **I** was recorded in $CDCl_3$, and the spectra of **III** and **IV**, in a $CDCl_3$–DMSO-d_6 mixture.
[b] For convenience, the atom numbering in the norpinane fragment of **I** is the same as in **III** and **IV**.

Table 2. ^{13}C NMR spectra of compounds **I**, **III**, and **IV**, δ_C, ppm[a]

Comp. no.	C^3	C^2, C^4	C^1, C^5	C^6	C^7	C=O	Ph
I[b]	13.8	25.5	44.1	52.8	91.0	154.1	127.2, 128.5, 128.6, 135.2
III	12.2	28.8	45.1	49.4	78.1	178.2	124.4, 125.5, 127.1, 142.1
IV	12.3	29.0	45.2	48.3	78.2	175.4	124.6, 125.7, 127.3, 142.1

[a] The spectrum of compound **I** was recorded in $CDCl_3$, and the spectra of **III** and **IV**, in a $CDCl_3$–DMSO-d_6 mixture.
[b] For convenience, the atom numbering in the norpinane fragment of **I** is the same as in **III** and **IV**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra of solutions in $CDCl_3$ and DMSO-d_6 were recorded on a Bruker DPX-300 instrument at 300.17 and 75.47 MHz, respectively. Silufol UV-254 plates were used for analytical TLC (eluent hexane–ether, 1 : 1). Elemental analyses were obtained on an HP-185B CHN analyzer. 7-Phenylbicyclo[3.1.1]heptane-6,7-carbolactone (**II**) (mp 75°C) was synthesized as described in [2].

7-Hydroxy-7-phenylbicyclo[3.1.1]heptane-6-carboxamide (III). A saturated solution of ammonia in methanol, 3 ml, was added to a solution of 0.214 g (1 mmol) of lactone **II** in 3 ml of methanol, and the mixture was stirred for 1–1.5 h at 25°C (the progress of the reaction was monitored by TLC). The solvent was distilled off, and the residue was purified by recrystallization. Yield 0.22 g (96%). mp 159°C (from methanol). R_f 0.17. Found, %: C 72.65, 72.74; H 7.33, 7.39; N 6.07, 6.12. $C_{14}H_{17}NO_2$. Calculated, %: C 72.70; H 7.41; N 6.06.

7-Hydroxy-7-phenylbicyclo[3.1.1]heptane-6-carbohydrazide (IV). Anhydrous hydrazine, 0.5 ml, was added to a solution of 0.214 g (1 mmol) of lactone **II** in 3 ml of methanol. The mixture was stirred for 1 h at room temperature until the reaction was complete (TLC). The solvent was distilled off, and the residue was chromatographically pure hydrazide **IV**. Yield 0.23 g (95%). mp 151°C (from methanol). R_f 0.14. Found, %: C 68.33, 6.30; H 7.38, 7.31; N 11.32, 11.29. $C_{14}H_{18}N_2O_2$. Calculated, %: C 68.27; H 7.37; N 11.37.

2-Phenyl-3-oxa-5-azatricyclo[4.4.0.0^{2,7}]decan-4-one (I). *a*. Powdered lead tetraacetate, 140 mg (0.315 mmol), was added to a solution of 70 mg (0.303 mmol) of amide **III** in 3 ml of anhydrous pyridine, and the resulting dark brown solution was stirred for 2.5–3 h at room temperature until the reaction was complete (TLC). Two drops of ethylene glycol were added to decompose excess $Pb(OAc)_4$, and the solvent was removed under reduced pressure. The residue was treated with 15 ml of methylene chloride and 5 ml of water. The organic phase was separated, washed with water (3 × 5 ml), and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 67 mg (97%) of chromatographically pure carbamate **I**.

b. Sodium nitrite, 63 mg (0.74 mmol), was added to a solution of 133 mg (0.54 mmol) of hydrazide **IV** in a mixture of 10 ml tetrahydrofuran and 10 ml of water. The solution was cooled to –10°C, 1.44 ml of 0.5 N hydrochloric acid was added, and the mixture was stirred for 20 min at –5°C. The resulting solution was transferred into a separatory funnel containing 30 ml of chloroform, and the mixture was vigorously shaken over a period of 5 min. The organic layer

was separated, and the aqueous layer was thoroughly extracted with chloroform. The extracts were combined with the organic phase, washed in succession with a 5% solution of sodium hydrogen carbonate (2×10 ml) and water (2×10 ml), and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 103 mg (83%) of chromatographically pure carbamate **I**. mp 148°C (from CCl_4). R_f 0.21. Found, %: C 73.26, 73.42; H 6.68, 6.61; N 6.07, 6.12. $C_{14}H_{15}NO_2$. Calculated, %: C 73.34; H 6.59; N 6.11.

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