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SHORT COMMUNICATIONS

Phase-transfer Catalysis in Alkylation of Ureas Containing Cage-like Fragments

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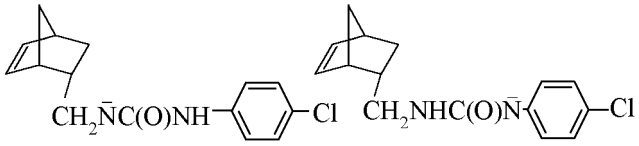
Nitrogen-containing compounds with cage-like fragments of norbornene, norbornane, and adamantane exhibit antiviral [1] and neurotropic [2] activity and thus are promising models for investigation of relations between the biological activity and the structure and stereochemistry of molecules. In the recent years the synthesis of these compounds is currently performed with the use of phase-transfer catalysis which plays a significant part in reactions with high sterical requirements to attacking reagents. Methods were developed for arylsulfonylation of amines [3], of alkylation and acylation of sulfonamides from the norbornene series [4].

In the present study we aimed at development of a procedure for alkylation of ureas from the norbornene series under conditions of the phase-transfer catalysis and investigation of the process chemoselectivity. Compound **II** was obtained from a stereochemically homogeneous amine **I** with the *endo*-orientation of the substituent in the norbornene fragment.

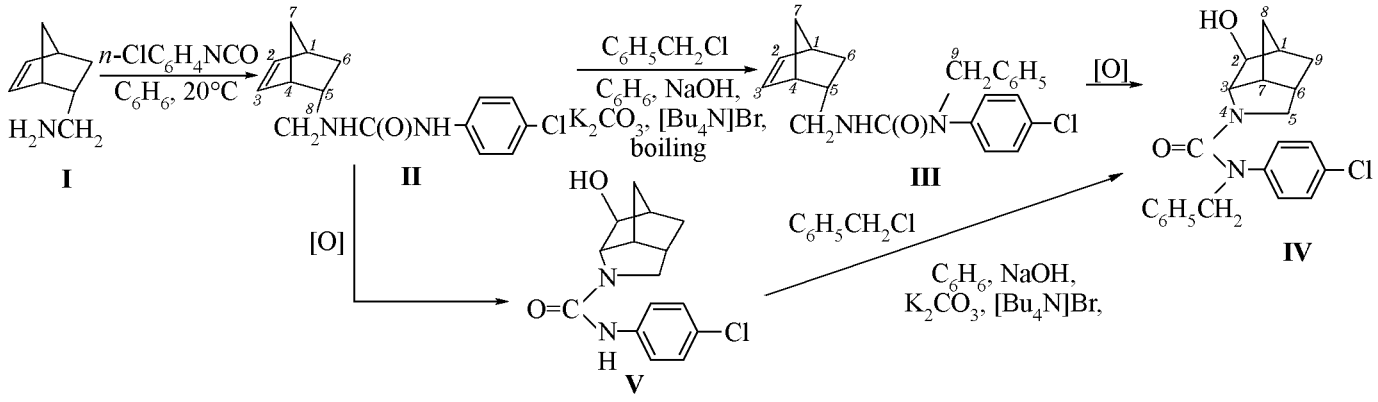
We failed to introduce a benzyl group into the urea moiety of compound **II** applying the conditions suitable for alkylation of sulfonamides from the norbornene series [4]: liquid–liquid system, benzene–10% water solution of sodium hydroxide, tetrabutylammonium chloride in amount of 10 to 100 mol%, 65–70°C. However we successfully carried out the reaction in a system solid–liquid in the presence of 50 mol% of the same catalyst.

The chemoselectivity of compound **II** alkylation was predicted by semiempirical quantum-chemical calculations (AM1, PM3) of proton affinity of intermediate anions: To anion **VIb** corresponded significantly smaller values (287.5 and 318.6 kJ mol^{-1} respectively) than to anion **VIa** (298.1 and 324.1 kJ mol^{-1} respectively).



VIa **VIb**

An additional chemical proof of the alkylation chemoselectivity was obtained by preparation of azabrendane **IV** by two ways: by oxidation of com-



I **II** **III** **IV** **V**

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pound **III** with peroxyphthalic acid, and by oxidation of compound **II** followed by alkylation of the heterocyclization product **V** with benzyl chloride under conditions of the phase-transfer catalysis. The formation of azabrendane systems was formerly demonstrated by an example of phenyl- and *m*-chlorophenyl-containing ureas [5], and also on an analog with *p*-tosyl substituent [6]. The structures of compounds **II**–**V** were confirmed by IR, ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra of azabrendanes **IV, V** appear characteristic proton signals of H^3 and H^2 (3.19, 3.27 ppm and 3.26, 3.42 ppm respectively). In the spectrum of compound **IV** are observed the signals of the benzyl group [4.75 ppm (2H) and 7.10–7.50 ppm (5H)]. Amine **I** was prepared by procedure [7], its characteristics were in agreement with the published data.

***N*-(Bicyclo[2.2.1]hept-5-en-2-endo-ylmethyl)-*N*'(4-chlorophenyl)urea (II).** To a solution of 0.15 g (0.001 mol) of *p*-chlorophenyl isocyanate in 5 ml of benzene was added 0.001 mol of amine **I** in 5 ml of benzene. The completion of reaction was determined by TLC. The precipitate formed was filtered off, washed with benzene, dried, and purified by recrystallization from aqueous 2-propanol. Yield 89%, mp 175–176°C. R_f (from ether) 0.76. IR spectrum, cm^{-1}: 3360, 3070, 1642, 1570, 1232, 910, 745, 735. ^{1}H NMR spectrum, δ, ppm: 6.08 d.d (H^2), 5.85 d.d (H^3), 2.94 d.d (H^{8A}), 2.87 d.d (H^{8B}), 2.73 m (H^1), 2.70 m (H^4), 2.16 m (H^5), 1.79 d.d (H^{6x}), 1.37 d (H^{7a}), 1.16 d (H^{7s}), 0.47 d.t (H^{6n}), 7.22 s, 6.89 t (NH), 8.01 d, 7.29 d.d, 7.25 d (H arom). Found, %: N 10.19. $C_{15}H_{17}ClN_2O$. Calculated, %: N 10.13.

***N*-Benzyl-*N*-(*p*-chlorophenyl)-*N*'-(bicyclo[2.2.1]-hept-5-en-2-endo-ylmethyl)urea (III).** To 0.37 g (0.001 mol) of compound **II** in 10 ml of anhydrous benzene was added 0.17 g (0.0005 mol, 50 mol%) of tetrabutylammonium bromide, 0.14 g (0.0035 mol) of powdered sodium hydroxide, 0.09 g (0.0006 mol) of crystalline sodium carbonate. The mixture was heated at stirring to 40°C for 2 h, then the temperature was raised to 60°C, and at vigorous stirring was added dropwise 0.13 g (0.001 mol, 0.12 ml) of benzyl chloride dissolved in 5 ml of anhydrous benzene. The temperature was raised to 70°C. The reaction progress was monitored by TLC. On completion of the reaction the mixture was cooled, twice washed with water, the water layer was thrice extracted with ether, the organic solutions were combined and dried with calcined $MgSO_4$, the solvent was removed, and the residue was subjected to column chromatography on silica gel (eluent ether). Yield 80%, mp 146–148°C. R_f (from ether) 0.74. IR spectrum, cm^{-1}: 3320, 3028, 1664, 1545, 1250, 1156, 730. ^{1}H NMR spectrum, δ, ppm: 6.07 d.d (H^2), 5.87 d.d (H^3), 4.25 ($2H^9$), 2.87 d.d (H^{8A}), 2.83 d.d (H^{8B}), 2.74 m (H^1), 2.70 m (H^4), 2.16 m (H^5), 1.73 d.d.d (H^{6x}), 1.35 d (H^{7s}), 1.20 d (H^{7a}), 0.49 d.t (H^{6n}), 4.46 t (NH), 7.13–6.94 (H arom). Found, %: N 7.70. $C_{22}H_{23}ClN_2O$. Calculated, %: N 7.64. Benzylation of azabrendane **V** was carried out by the same procedure.

***N*-Benzyl-*N*-(*p*-chlorophenyl)-*exo*-2-hydroxy-4-azatricyclo-[4.2.1.0^{3,7}]nonane-4-carboxamide (IV),** yield 75.6%, mp 198–199°C. R_f (from ether) 0.76. IR spectrum, cm^{-1}: 3386, 3050, 1618, 1540, 1252, 1100, 1030. ^{1}H NMR spectrum, δ, ppm: 4.75 ($2H^{10}$), 3.55 d.d (H^{5A}), 3.40 d. (H^{5B}), 3.26 s. (H^2), 3.19 d (H^3), 2.57 m (H^7), 2.30 m (H^6), 2.20 m (H^1), 1.97 d (H^{8s}), 1.87 m (H^{9x}), 1.38 d. (H^{8a}), 0.79 d (H^{9n}), 7.50–7.10 (H arom). Found, %: N 7.37. $C_{22}H_{23}ClN_2O_2$. Calculated, %: N 7.32.

(*p*-Chlorophenyl)-*exo*-2-hydroxy-4-azatricyclo-[4.2.1.0^{3,7}]nonane-4-carboxamide (V). To a suspension of 0.56 g (0.0015 mol) of compound **II**, 0.04 g (0.00075 mol) of carbamide, and 0.31 g (0.29 ml, 0.003 mol) of 35% water solution of hydrogen peroxide in 10 ml of ethyl acetate was added at stirring (20–25°C) 0.44 g (0.003 mol) of phthalic anhydride, and the stirring was continued till completion of the reaction (TLC monitoring). The mixture was treated with saturated solution of sodium hydrogen carbonate, the organic layer was separated and dried with calcined $MgSO_4$. The solvent was removed, the reaction product was crystallized from aqueous 2-propanol, yield 90%, mp 162–164°C. R_f (from ether) 0.80. IR spectrum, cm^{-1}: 3445, 3160, 3040, 1645, 1550, 1270, 1125, 1041. ^{1}H NMR spectrum, δ, ppm: 6.64 (H^{10}), 3.51 d.d (H^{5A}), 3.42 s (H^2), 3.40 d (H^{5B}), 3.27 d (H^3), 2.62 m (H^7), 2.30 m (H^6), 2.15 m (H^1), 1.97 d (H^{8s}), 1.89 m (H^{9x}), 1.43 d (H^{8a}), 0.85 d (H^{9n}), 7.70 s (NH), 7.50 d, 7.27 d, (H arom). Found, %: N 9.50. $C_{15}H_{17}N_2O_2Cl$. Calculated, %: N 9.57.

By the same procedure the oxidation of compound **III** was performed to afford azabrendane **IV** in 74.1% yield identical to the above described sample.

IR spectra were recorded on spectrophotometer Specord 75-IR from samples pelletized with KBr. ^{1}H NMR spectra were registered on spectrometers Bruker at operating frequencies 200 and 500 MHz from solutions of compounds in deuterochloroform, internal reference HMDS. The reaction progress was

followed and the purity of compounds obtained was checked by TLC on Silicagel 60 F 254 plates, eluent ether, development in iodine vapor. Elemental analyses were carried out on Karlo Erba analyzer.

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