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On nucleophilic substitution reaction of 2α-/1--tosyloxyethyl/-5,5-dimethylbicyclo[2.1.1] hexane

Reakcja podstawienia nukleofilowego 2α-(1-tosyloksyetylo)-5,5--dimetylobicyklo[2.1.1] heksanu

Azidolysis and cyanolysis reactions of 2α-(1-tosyloxyethyl)-5,5-dimethylbicyclo [2.1.1] hexane (**3**) leading to 2α-(1-azidoethyl)-5,5-dimethyl–bicyclo [2.1.1] hexane (**4**) and 2α-(1-cyanoethyl)-5,5-dimethylbicyclo [2.1.1] hexane (7) respectively, have been examined. The structures of the compounds obtained were established on the basis of spectral analysis (IR, ^{1}H NMR) and by mutual chemical transformations.

In the course of almost hundred years of investigations on bicyclo [2.1.1] hexane (**1**), only few papers [1–12] were fully devoted to the chemistry of this system. Most of the published papers described the derivatives of **1** as by--products obtained in reactions of pinane derivatives.

Scheme 1

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Moreover, the investigations on nitrogen derivatives of **1** as well as on nucleophilic substitution of bicyclo [2.1.1] hexane were very rare [4]. In continuation of our interest in this highly strained bicyclic system [11–14] , we have obtained some new derivatives of **1** starting from easily accessible tosylate of alcohol **2** i.e. 2α-(1-hydroxyethyl)-5,5-dimethylbicyclo [2.1.1] hexane [12].

All the described transformations of starting tosylate **3** were carried out on three optical forms of **3** i.e. (+), (–) and (±). This way of synthesis let us establish without any doubts full stereochemistry of compounds obtained as well as the mechanism of realized reactions.

The starting material i.e. (+), (–) or (±) tosylate **3** was obtained in every case from (–), (+) or (±) from α-pinene, respectively, by the methods described earlier [12,15].

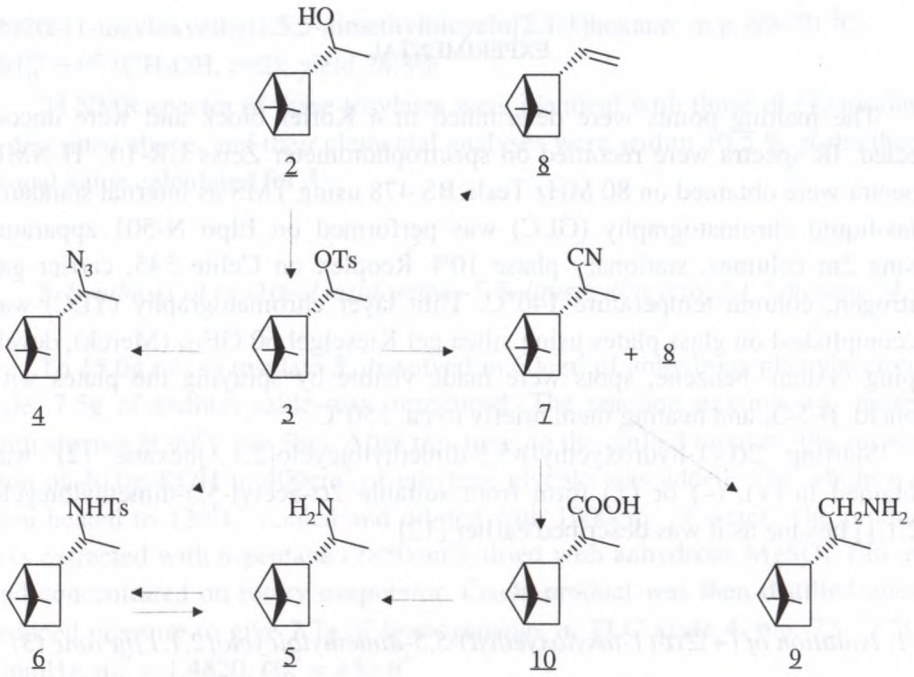
Tosylate **3** subjected to the azidolysis gave azidoderivative **4**, which after reduction by LAH in ether was transformed into amine **5**. The amine **5** was next transformed into tosylamide **6**, which after crystallization was hydrolyzed giving homogeneous sample of **5**, the structure of which was fully confirmed by the analysis.

Cyanolysis of tosylate **3** gave two products: cyanoderivative **7** and vinylderivative **8**. The latter, being the product of elimination reaction, appeared to be identical with vinylderivative **8** obtained in 25% of yield in the reaction of **3** with t-BuOK.

Cyanoderivative **7** after reduction by LAH in ether gave suitable amine **9**, while the hydrolysis of **7** furnished the acid **10**, which in Schmidt reaction gave the amine **5** identical in all aspects with that obtained after hydrolysis of tosylamide **6**.

The results of our literature studies showed that the compounds **3–10** were not previously described in the chemical literature.

All the structures were confirmed by elemental analyses and spectral data (see experimental). The mutual transformations of compounds obtained additionally supported their structures.



Scheme 2

The crucial reactions i.e. cyanolysis and azidolysis of tosylate **3** were carried out in conditions in which transformations of carbon skeleton of bicyclic system (mainly opening of cyclobutane ring) were limited to minimum by using aprotic solvents. In the case of cyanoderivative **7** the yield of the reaction carried out in DMSO was satisfactory (51.5 %).

In the case of reaction of azidolysis of tosylate **3** in the same solvent, the yield of azidoderivative **4** was low (13.8 %) and we used phenylacetonitrile instead of DMSO. After many trials of work up, connected with the difficulties in separation of the product obtained from the solvent used, we decided to carry out mild hydrolysis of phenylacetonitrile, which after alkalic work up, was separated giving the expected product **4** in high yield of 89.5 %.

The described transformations constitute the convenient method of synthesis of the compounds of potential importance in search of pharmacologically active compounds with strained systems in the molecules.

EXPERIMENTAL

The melting points were determined in a Kofler block and were uncorrected. IR spectra were recorded on spectrophotometer Zeiss UR-10. ^{1}H NMR spectra were obtained on 80 MHz Tesla BS 478 using TMS as internal standard. Gas-liquid chromatography (GLC) was performed on Elpo N-501 apparatus using 2m columns, stationary phase 10% Reoplex on Celite 545, carrier gas nitrogen, column temperature 140°C. Thin layer chromatography (TLC) was accomplished on glass plates using silica gel Kieselgel 60 GF_{254} (Merck), developing system: benzene, spots were made visible by spraying the plates with conctd. H_2SO_4 and heating them briefly to ca. 250°C.

Starting 2α-(1-hydroxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane (**2**) was obtained in (+), (–) or (±) form from suitable 2α-acetyl-5,5-dimethylbicyclo [2.1.1] hexane as it was described earlier [12].

*1. Isolation of (+)2α-(1-tosyloxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane (**3**)*

To 45.3g of crude 2α-acetyl-5,5-dimethylbicyclo[2.1.1]hexane dissolved in 450cm^3 of Et_2O, the solution of 5.0g of LAH was introduced. The mixture was heated to boil for 8hrs and worked up in the usual way giving 41.7g of crude alcohol **2**, b.p.=70–74 °C/2.5mmHg. This product was next tosylated by means of p-toluenesulfochloride in pyridine [15] to give 28.2g (29.1% of yield) of (+)2α-(1-tosyloxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane (**3**).

After crystallization from n-heptane, homogeneous in TLC tosylate **3** showed m.p. 69–70 °C, $[\alpha]_D^{20}$ = +32.5° (CH_3OH, c=2).

^{1}H NMR ($CDCl_3$), δ: 0.8 (s, 3H), 1.2 (s, 3H), 1.3 (d, 3H, J=7 Hz), 1.5 (m, 7H), 2.45 (s, 3H, $C\underline{H_3}$-Ar), 4.5 (m, 1H), 7.3 (d, 2H, J=7 Hz, Ar), 7.8 (d,2H, 7 Hz, Ar).

Analysis for $C_{17}H_{24}SO_3$ (308.4) calcd.: 66.2% C, 7.8% H, 10.4% S
found: 65.8% C, 7.9% H, 10.3% S

In the same manner (–) and (±) tosylates were obtained:
(–)2α-(1-tosyloxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane: m.p. 69–70 °C, $[\alpha]_D^{20}$=-32.5°(CH_3OH, c=2), yield 29.3%.

(±)2α-(1-tosyloxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane: m.p. 69–70 °C, $[\alpha]_D^{20} = 0°$ (CH_3OH, c=2), yield 28.8%.

^1H NMR spectra of these tosylates were identical with those of (+) tosylate **3** described above, and their elemental analyses were within ±0.5 % of the theoretical value calculated for **3**.

2. Synthesis of (+)2α-(1-azidoethyl)-5,5-dimethylbicyclo[2.1.1]hexane (4)

To 15.0g of (+) tosylate **3**, dissolved in 60cm^3 of anhydrous phenylacetonitrile, 7.5g of sodium azide was introduced. The reaction mixture was heated with stirring at 90°C for 5hrs. After this time, to the chilled mixture, the suspension of 40.0g KOH in 400cm^3 of ethylene glycole was added. The whole was then heated to 120°C, cooled and diluted with 1000cm^3 of water. The product was extracted with *n*-pentane (7×50cm^3), dried with anhydrous $MgSO_4$, filtered and concentrated on rotary evaporator. Crude product was then distilled under reduced pressure to give 7.7g of homogeneous in TLC azide **4**, b.p. 72–73 °C/ 3mmHg, $n_D^{20} = 1.4820$, $\alpha_D^{20} = +53.6°$.

IR (liquid film), cm^{-1}: 2920 (–CH_2), 2200 (–N_3), 1385–1365 (gem. –CH_3).

^1H NMR (CCl_4), δ: 0.8 (s, 3H), 1.2 (s, 3H), 1.3 (d, 3H, J=6 Hz), 3.6(m, 1H, HC-N_3), 1.02.1 (m, 7H).

In the same manner (–) and (±) azides **4** were obtained from (–) and (±) tosylates **3** respectively, and they had physical and spectral properties identical with these of (+) **3**, with the exception of the sign of optical rotation i.e. $\alpha_D^{20} = -53.6°$ for levorotatory and 0° for racemic ones.

3. Isolation of (+)2α-(1-p-toluenesulfonamidoethyl)-5,5-dimethylbicyclo-[2.1.1]hexane (6)

To 5.0g of (+) azide **4** dissolved in 100cm^3 of anhydrous diethyl ether, 1.5g of LAH in 30cm^3 of anhydrous diethyl ether was added. The reaction was carried out for 4 hrs in boiling ether, cooled and carefully diluted with water to precipitation of white precipitate, which was next filtered off.

The solution of amine obtained was then dried over anhydrous $MgSO_4$, and after distilling off the solvent, 3.0g of oily product was obtained. This product was next dissolved in 10cm^3 of anhydrous pyridine and after cooling with ice,

treated with 8.0g of *p*-toluenesulfochloride. After 6 hrs the whole was diluted with 100cm^3 of H_2O giving the precipitate which was filtered, dried and crystallized from methanol yielding 6.2g (72.1%) of *p*-toluenesulfonamide **6**: m.p. 123°C
$[\alpha]_D^{20}$ = +28.4° (CH_3OH, c=2)

Analysis for $C_{17}H_{25}NO_2S$ (307.4) calcd.: 66.5% C, 8.2% H, 4.6% N, 10.4% S
found: 66.5% C, 8.4% H, 4.5% N, 10.6% S

IR (KBr), cm^{-1}: 3500 (–NH), 2920(–CH_2), 1385–1365 (gem. –CH_3).

^{1}H NMR (CCl_4), δ: 0.7 (s, 3H), 0.9 (d, 3H, J=6Hz, –CH_3), 1.1 (s, 3H, -CH_3), 1.2–2.1(m, 7H), 2.4 (s, 3H, CH_3–Ar), 3.0 (m, 1H, CH–N), 5.6 (d, 1H, J=6Hz), 7.2 (d, 2H, J=7Hz Ar), 7.8 (d, 2H, J=7 Hz, Ar).

*4. Isolation of (+)2α-(1-aminoethyl)-5,5-dimethylbicyclo[2.1.1]hexane (**5**)*

To 10g of (+)-p-toluenesulfonamide **6** dissolved in 150cm^3 of anhydrous ethylamine at temperature 0°C, 3.5g of scrumbled lithium was introduced. The whole was kept in boil for ca. 8 hrs (till stable dark blue coloration of the solution). Next, the ethylamine was distilled off, and to the residue 100cm^3 of water was added. Ethereal layer was separated, dried over anhydrous $MgSO_4$, and solvent was distilled off. The residue was next distilled under reduced pressure giving 3.5g (70.1%) of homogeneous in TLC amine **5** b.p. 86°C/4mm Hg,
n_D^{20} = 1.4760, α_D^{20} = +17.4°

IR (liquid film), cm^{-1}: 3350 (–NH_2), 1385–1365 (gem. –CH_3).

^{1}H NMR (CCl_4), δ: 0.8 (s, 3H),1.0 (d, 3H, J=6Hz), 1.2 (s, 3H), 2.5(m, 2H), 1.2–2.0 (m, 8H).

*5. Synthesis of (+)2α-(1-cyanoethyl)-5,5-dimethylbicyclo[2.1.1]hexane (**7**)*

To the solution of 25.0g of tosylate **3** in 250cm^3 of DMSO, 12.5g of powdered potassium cyanide was added. The whole was stirred at 85°C for 3 hrs and after this time cooled, diluted with 900cm^3 of water and extracted with *n*-pentane (4×50cm^3). Combined pentane extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was distilled off. Crude product (10.3g) ap-

peared to be the mixture of two components (GLC), and was subjected to the fractional distillation under reduced pressure. The following fractions were obtained:

a) 2α-vinyl-5,5-dimethylbicyclo[2.1.1]hexane (**8**): 1.8g (17.6%), b.p. 53°C/ 10mmHg,
n_D^{20} = 1.4705, α_D^{20} = +19.5°, IR and ^{1}H NMR spectra are described in p.6

b) (+)-2α-(1-cyanoethyl)-5,5-dimethylbicyclo[2.1.1]hexane (**7**): 5.7g (43.2%), b.p. 84°C/5mmHg, n_D^{20} = 1.4565, α_D^{20} = +23.2°,
IR (liquid film), cm^{-1}: 2920 (–CH_2), 2100 (–CN), 1385–1365 (gem. –CH_3).
^{1}H NMR ($CDCl_3$), δ: 0.9 (s, 3H), 1.2 (s, 3H), 1.4 (d, 3H, J=6 Hz), 1.2–2.1 (m, 7H), 3.2 (m, 1H)

Analysis for $C_{11}H_{17}N$ (163.3) calcd.: 80.9% C, 10.5% H, 8.6% N
found: 81.3% C, 10.8% H, 8.7% N

6. Synthesis of (+)2α-vinyl-5,5-dimethylbicyclo[2.1.1]hexane (8)

To 25.0g of (+) tosylate **3** dissolved in 250cm^3 of anhydrous DMSO, 20g of pure potassium *t*-butanolate was added. The reaction mixture was stirred for 3 hrs at 80°C. After this time the mixture was cooled, diluted with 1000cm^3 of water and extracted with *n*-pentane (5×40cm^3). Combined pentane extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was distilled off to give an oily product, which was distilled under reduced pressure yielding 2.6g (25.5%) of vinyl derivative **8**, identical in all respects with that described in p.5.: b.p. 53° C/ 10mmHg, n_D^{20} = 1.4705, α_D^{20} = +19.5°,
IR (liquid film), cm^{-1}: 3040, 1630 (C=C), 2920 (–CH_2), 1385–1365 (gem. –CH_3).
^{1}H NMR ($CDCl_3$), δ: 1.0 (s, 6H, gem. CH_3), 2.7 (m, 1H), 4.6 (d, 2H, J=16 Hz), 0.8–1.6 (m, 7H),

Analysis for $C_{10}H_{16}$ (136.2) calcd.: 88.2% C, 11.8% H
found: 88.0% C, 11.6% H

7. Reduction of (+)2α-(1-cyanoethyl)-5,5-dimethylbicyclo[2.1.1]hexane (7) by means of LAH

To a solution of 3.0g cyanoderivative **7** dissolved in 60cm^3 of anhydrous ether, 0.9g of LAH dissolved in 20cm^3 of ether was introduced. The reaction was carried on at boil for 6 hrs. After this time, the whole was cooled and 2cm^3 of water were carefully introduced with stirring.

The product was then isolated by steam distillation. Organic and aqueous layers were next separated and the aqueous one was extracted additionally with ether. Combined ethereal extracts were washed with 1% solution of sulfuric acid, and next with water and aqueous solution of amine sulfate was treated with excess of solid potassium hydroxide to give the amine, which was then extracted with ether and dried over solid potassium hydroxide. After filtration of drying agent, the solution was concentrated and the product was subjected to the distillation under reduced pressure giving 1.8g of homogeneous in TLC 2α-(2-amino-1-methylethyl)-5,5-dimethylbicyclo[2.1.1]hexane (**9**) (58% of yield): b.p. 91–92 °C/ 3mmHg, $n_D^{20} = 1.4785$, $\alpha_D^{20} = +11.3°$

IR (liquid film), cm^{-1}: 3400–3300 (NH_2), 2920 ($-CH_2$), 1385–1365 (gem. $-CH_3$).

^{1}H NMR ($CDCl_3$), δ: 0.9 (s, 3H, $-CH_3$), 1.1 (s, 3H, $-CH_3$), 1.2 (d, 3H, J=6Hz), 2.5 (m, 2H, NH_2 –signal disappears after deutering), 1.3–2.2 (m, 10H).

Analysis for $C_{11}H_{21}N$ (167.3) calcd.: 79.0% C, 12.7% H
found: 79.0% C, 12.4% H

8. Alkaline hydrolysis of (+)2α-(1-cyanoethyl)-5,5-dimethylbicyclo [2.1.1]hexane (7)

The mixture of 10g of nitrile **7** and 10g of potassium hydroxide in 90g of ethylene glycole was heated to boil (approx. 185°C) under air reflux condenser for 40hrs. During this reaction evolution of NH_3 was observed. After this time the whole was cooled, diluted with 500cm^3 of water and extracted with diethylether (3x50cm^3). The aqueous layer of potassium salt was next acidified with 10% of sulfuric acid and the product was extracted with diethyl ether (4x50cm^3). Combined ethereal extracts were washed with water, dried over

anhydrous $MgSO_4$ and after filtration of drying agent, concentrated to dryness. The solid product after crystallization from hexane gave 7.4g (66.1% of yield) of crystalline acid **10**, m.p. 63–64 °C, $[\alpha]_D^{20}$ = -14.1° ($CHCl_3$, c=2)

IR (KBr), cm^{-1}: 3100 (–COOH), 2920 (=CH_2), 1700 (=CO), 1385–1365 (gem. –CH_3).

^1H NMR ($CDCl_3$), δ: 0.8 (s, 3H, CH_3), 0.9 (s, 3H, CH_3), 1.2 (d, 3H, J=7Hz, –CH_3), 1.2–2.6 (m, 9H).

Analysis for $C_{11}H_{18}O_2$ (182.2) calcd.: 72.5% C, 9.95% H
found: 72.8% C, 10.3% H

9. Degradation of (-)2α-(1-carboxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane ***(10)***

To a mixture of 5.0g of acid **10** and 100cm^3 of anhydrous sulfuric acid dissolved in 250cm^3 of methylene chloride, 6.5g of sodium azide was introduced with stirring at 45°C. The reaction was then stirred for 30min. at 55°C. After this time, to the cooled mixture ice was introduced and then 10% solution of NaOH was added to alkaline reaction. Two layers were next separated and the aqueous one was extracted with ether (3×50cm^3). Combined methylene chloride and ethereal extracts were dried over anhydrous $MgSO_4$, filtered off and after distillation of the solvents they were subjected to distillation under reduced pressure.

As a result of distillation 1.6g (38.1%) of (+)-2α-(1-aminoethyl)-5,5--dimethylbicyclo[2.1.1]hexane (**5**) was obtained, which appeared to be identical in all aspects with the preparation described in p.4. This amine gave tosylate m.p. 123°C, which did not have any m.p. depression after mixing with amide **6** described in p.3.

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STRESZCZENIE

Przebadano reakcje azydolizy i cyjanolizy 2α-(1-tosyloksyetyl-5,5-dimetylobicyklo-[2.1.1]-heksanu (**3**) uzyskując odpowiednio 2α-(1-azydoetylo)-5,5dimetylobicyklo[2.1.1]heksan (**4**) oraz 2α-(1-cyjanoetylo)-5,5-dimetylobicyklo[2.1.1]heksan (**7**). Budowę otrzymanych związków ustalono na podstawie analizy spektralnej oraz w drodze przemian chemicznych.

NAZWY WZORÓW

Wzór nr 1: 5,5-dimethylbicyclo[2.1.1]hexane
Wzór nr 2: 2α-(1-hydroxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane
Wzór nr 3: 2α-(1-tosyloxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane
Wzór nr 4: 2α-(1-azidoethyl)-5,5-dimethylbicyclo[2.1.1]hexane
Wzór nr 5: 2α-(1-aminoethyl) -5,5-dimethylbicyclo[2.1.1]hexane
Wzór nr 6: 2α-(1-p-toluenesulfonamidoethyl)-5,5-dimethylbicyclo[2.1.1] hexane
Wzór nr 7: 2α-(1-cyanoethyl)-5,5-dimethylbicyclo[2.1.1]hexane
Wzór nr 8: 2α-vinyl-5,5-dimethylbicyclo[2.1.1]hexane
Wzór nr 9: 2α-(2-amino-1-methylethyl)-5,5-dimethylbicyclo[2.1.1]hexane
Wzór nr 10: 2α-(1-carboxyethyl)-5,5-dimethylbicyclo[2.1.1]hexane