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Reaction of (+) Dihydroxycarveol Tosylate with KCN in Apriotic Solvents (-)(1S,2R,4S) 1-Methyl-4-isopropenylcyclohexane-2-carbonitrile

Reakcja (+) tosylanu dihydrokarweolu z KCN w rozpuszczalnikach aprotycznych. (–) (1S,2R,4S) 1 metylo-4-izopropenylocykloheksylo-2-karbonitryl

Reaction of (+) dihydroxycarveol tosylate with KCN in pyridine and DMF solutions were proved to produce a mixture of hydrocarbons. However, in DMSO sterically homogeneous (–)(1S,2R,4S) 1-methyl-4-isopropenylcyclo–hexane-2-carbonitrile [(–)neodihydrocarvylcarbonitrile] was the main reaction product. The structure of the compound obtained was determined on the basis of spectral data, elemental analysis, and the chemical transformations which indicated configurational relation of the title compound the known (–)(1S,2R,4S) 1-methyl-4-isopropylcyclohexyl-2methylenamine.

The application of aprotic solvents [1–3] in organic chemistry afforded new synthetic possibilities. First reports by N a c e [4], C r a m et al. [5] and by B o r o w i e c k i and C h r é t i e n – B e s s i è r e [6] related to the behavior of terpene compounds in the solvents of this type prompted us to further investigations on their applications in terpene chemistry. Some interesting results of isomerization [7], elimination [8], and substitution reactions with azides anions [9], and cyanides [10] carried out on terpene tosylates were the origin of investigations on the reaction of (+) dihydrocarveol tosylate (1) with KCN in aprotic solvents. The expected introduction of –CN group to a molecule of terpene

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compound allow to obtain novel derivatives, and among them, compounds of potential biological activity. Many of terpene compounds show such properties [11].

1. RESULTS AND DISCUSSION

Reactions of (+) dihydrocarveol tosylate (1) [(+)(1S,2S,4S)*p*-ment-8-(9)-en-ol-2 tosylate] [12,13] with KCN were carried out in pyridine, DMF, and DMSO. The choice of solvent used was independent of usefulness of pyridine and DMF in isomerization of terpene epoxy compounds [7]. However, the application of DMSO was highly successful in eliminations [8] and substitutions of terpene tosylates

Reaction of (1) with KCN in pyridine solution afforded a mixture of limonene (2) and isolimonene (3) (85:15) in 20.9% yield. In DMF solution also mixture of hydrocarbon (2) and (3) have been formed in 47.7% yield (80:20). According to the previous investigations of the effects of aprotic solvents on substitution reactions [14–16] in both cases, particulary when the reaction was carried out in DMF, formation of substitution, and not elimination product was expected. Only the application of DMSO allowed to obtain the expected result, although in this case also elimination competed with substitution reaction (Fig. 1). Because any detectable amounts of terpene alcohols were not reported for the reaction of substitution of tosyloxy group by azide [9] one, it was surprising that some amount of (–)neodihydrocarvenol (4) was found in our reaction. On the other hand, this unexpected fact is not completely unusual because formation of terpene alcohols during cyanolysis of (+)carvomenthol tosylate [10a], (–)cis-carane-trans-4-ol tosylate [10b] and (+)trans-tosyloxy-2-cis-dihydropyrole [10c] as by-product was observed. The authors of these reports have mentioned only the fact of obtention of alcohols, but they did not discuss the mechanism of their formation. The application in all cases the anhydrous solvents (especially emphasized by the authors) indicate the complex run of the reaction and not the simple hydrolysis of the tosylates. The main reaction product, i.e. (–)(1S,2R,4S) 1-methyl-4-isopropenylcyclohexane-2-carbonitrile [(-)neodihydrocarvylcarbonitrile] (5) was present in 82% yield in the crude reaction mixture, and was isolated as a chromatographically pure substance in 56% yield.

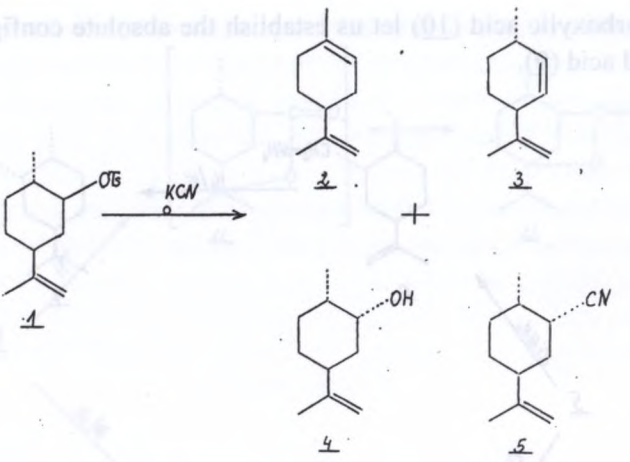

Fig. 1. 1 – (+) Dihydrocarveol tosylate, 2 – Limonene, 3 – Izolimonene, 4 – Neodihydrocarveol, 5 – (–) Neodihydrocarvylcarbonitrile

Substitution reaction may be stereospecific one with the inversion of the configuration at the attacked carbon atom (S_N2 reaction type) or non-stereospecific one, which affords, not exclusively, but only predominantly the thermodynamically favored form (S_N1 reaction type).

Although TLC indicated the homogeneity of nitrile (5), for statement of the fact as certain, stronger evidences were required. Also for the configuration of the obtained compound (5) a series of confirmations was necessary. Reduction of nitrile (5) with $LiAlH_4$ (Fig. 2) afforded chromatographically pure (-)(1S,2R,4S) 1-methyl-isopropenylcyclohexyl-2-methyleneamine [(-)neodihydrocarvylmethyleneamine] (6) which on catalytic reduction afforded the known [10a] (–)(1S,2R,4S) 1-methyl-4-isopropylcyclohexyl-2-methyleneamine [(–)neocarvomenthylmethyleneamine] (7). Alkaline hydrolysis of nitrile (5) (Fig. 2) afforded a mixture of (+)(1S,2S,4S) 1-methyl-4-isopropenylcyclohexyl-2-carboxamide (8) and (+)(1S,2S,4S) 1-methyl-4-isopropenylcyclohexane-2-carboxylic acid [(+)dihydrocarvylformic acid] (9). In both cases configuration at C_2 of the cyclohexane ring is equatorial, i.e. thermodynamically favoured, since the alkaline medium promotes formation of the planar carbanion at C_2 placed at position relatively to the carbonyl group. The mentioned above transformations were already used in synthesis of epimeric acids [17]. Catalytic reduction of acid (9) to known [10a] (+)(1S,2S,4S) 1-methyl-4-isopropylcyclo-

hexyl-2-carboxylic acid (10) let us establish the absolute configurations of amide (8) and acid (9).

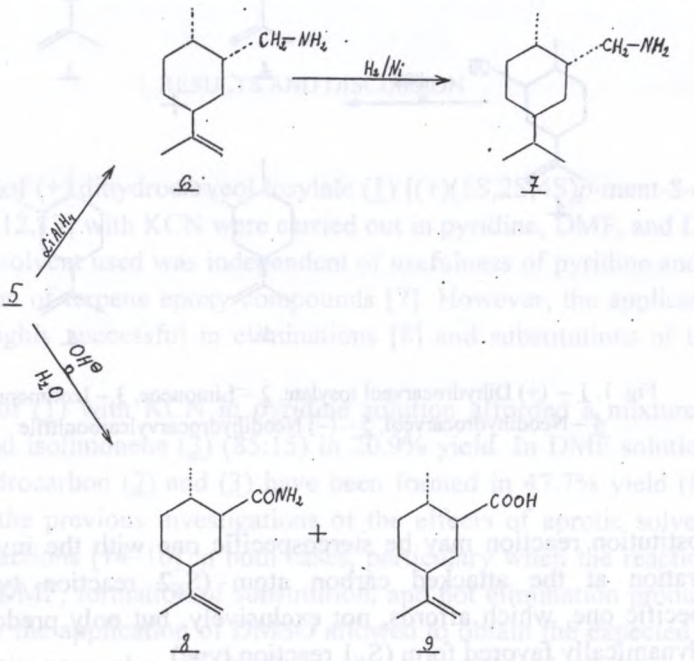

Fig. 2. 5 – (–) Neodihydrocarvylcarbonitrile, 6 – (–) Neodihydrocarvylmethyleneamine, 7 – (–) Neocarvomenthylmethyleneamine, 8 – (+)(1S,2S,4S) 1-Methyl-4-isopropenylcyclohexyl-2-carboxamide, 9 – (+) Dihydrocarvylformic acid

Acidic hydrolysis of nitrile (5), which should perform without change of configuration of carbon skeleton, gave unfortunately tarry substance, obtained probably as a result of polymerization of double bonds. However, the fact of obtaining of amins (7) during the twice reduction of nitrile (5) is a sufficient proof for its stereochemical structure. Tests of delicate acidic hydrolysis did not give satisfactory results. From our point of view the study of behavior of acid (9) in the presence of dilute sulfuric acid could be interesting. We assumed the possibility of formation of 4,4,8-trimethyl-3-oxabicyclo-[3,3,1]-nonan-2-on (11) as a result of hydration of double bond in molecule of acid (9), and next lactone formation from the hydroxyacid.

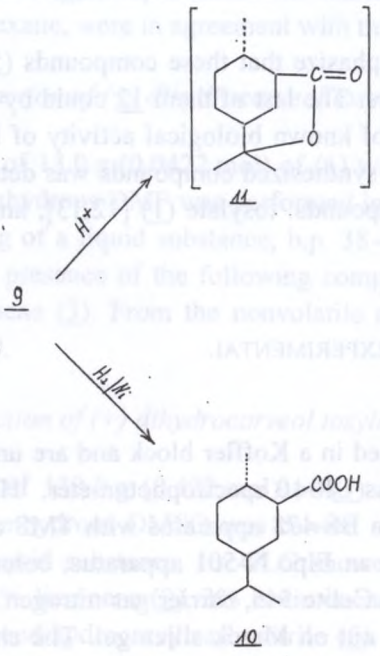

Fig. 3. 9 – (+) Dihydrocarvylformic acid, 10 – (+)(1S,2S,4S) 1-Methyl-4-isopropylcyclohexyl-2-carboxylic acid, 11 – 4,4,8-Trimethyl-3-oxobicyclo-[3.3.1]-nonan-2-one, 12 – 7-Methyl-4-isopropyl-3-oxobicyclo-[3.2.1]-octan-2-one

In fact, during this reaction the compound showing lacton's character was found. However, we did not find two singlets of methyl groups in the ^{1}HNMR spectrum supposed for lactone (11). On the other hand, the presence in this spectrum of three doublets from three methyl groups attached to tertiary carbon atoms have decided about the admission of the structure of lactone represented by the formula (12). Probably at first the lactone (11) is formed and next the rearrangement to 7-methyl-4-isopropyl-3-oxo-bicyclo-[3.2.1]-octanone-2 (12) takes place. Consideration of molecular models shows that lactone (12) has a more flexible structure. One can take into consideration the formation of lactone (12) during isomerisation of double bond followed by lactone formation reactions. However, displacement of double bond C_8-C_9 into C_4-C_8 position in trans *p*-menthane seems to be less probable. These considerations may be supported by the fact of acidic isomerisation of α-pinene in which the limonene,

containing stable C_8-C_9 double bond was obtained as a main reaction product [18].

In conclusion we want to emphasize that these compounds (5, 6, 8, 9 and 12) were not described in literature. The last of them 12 could by very interesting for pharmacologists because of known biological activity of lactones [19]. The absolute configuration of the synthesized compounds was determined from known structure of the inital compounds: tosylate (1) [12,13], amine (7) [10a] and acid (10) [10a].

2. EXPERIMENTAL

Melting points were determined in a Koffler block and are uncorrected. IR spectra were recorded on the Zeiss UR-10 spectrophotometer. ^{1}HNMR spectra were performed on 80 MHz Tesla BS-478 apparatus with TMS as an internal standard. GLC was performed on an Elpo N-501 apparatus, column 2 m long, stationary phase 10%. Reoplex on Celite 545, carrier gas nitrogen, column temperature 140°C. TLC was carried out on Merck silica gel. The chromatograms were developed with benzene–methanol (19:1) and visualized by spraying with concentrated H_2SO_4 and heating at 250°C. (+)Dihydrocarveol tosylate (1) m.p. 65°C was prepared according to K o z i n a and D a n i l o v [12]. Standards for chromatography, i.e. limonen (2) b.p. 64,5°C/15 mm Hg, $[\alpha]_D^{20}$ = 1,4722, was prepared with commercial oleum carvil, isolimonen (3) was prepared according to P i g u l e w s k i [20], neodihydrocarveol (4) was prepared according to K u c z y ń s k i and P i ą t k o w s k i [21].

1. Reaction of (+) dihydrocarveol tosylate (1) with KCN in pyridine

To a solution containing 13.0 g (0.0422 mol) of compound (1) in 130 ccm of anhydrous pyridine 6.5 g (0.0985 mol) of powdered KCN was added. The whole under vigorous stirring was heated at 80–85°C for 8 hrs.

The cooled reaction mixture was diluted with fivefold volume of water and extracted with *n*-penthane (5 × 100 ccm). The combined extracted were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure the residue was distilled under reduced pressure and afforded 1.2 g of a liquid substance, b.p. 38–40°C/4 mmHg, $[\alpha]_D^{20}$ = 1.4714, $[\alpha]_D^{20}$ = -83.0° IR (neat), ν_{max}:3040 cm^{-1} (>C=C<), GLC of the latter indicated the presence of 85% of limonene (3) and

15% isolimonene (3). Properties of non-volatile residue (9,6 g) after crystallization from *n*-hexane, were in agreement with those of starting tosylate (1).

2. Reaction of (+) dihydrocarveol tosylate (1) with KCN in DMF

Reaction of 13.0 g (0,0422 mol) of (1) with 6.5 g (0.0985 mol) of KCN in 130 ccm of anhydrous DMF was performed in an analogous manner as in. p. 1., to afford 2.7 g of a liquid substance, b.p. 38–40°C/4 mmHg. GLC of the latter displayed the presence of the following compounds: 80% of limonene (2) and 20% isolimonene (3). From the nonvolatile residue 7.9 g starting tosylate (1) was recovered.

3. Reaction of (+) dihydrocarveol tosylate (1) with KCN in DMSO

Reaction of 130.0 g (0.422 mol) of (1) with 65.0 g (0.985 mol) KCN in 1300 ccm of anhydrous DMSO was carried out similarly as in p. 1., to afford 53.0 g of a liquid substance. Its GLC showed the presence of the following compounds: 4% limonene (2), 3% isolimonene (3), 11% neodihydrocarveol (4) and 82% (–)neodihydrocarvylcarbonitrile (5). The crude mixture of the above mentioned products was fractionally distilled under reduced pressure to produce the fractions: (I) 9.2 g; b.p. 40–76°C/4 mmHg; (II) 41.1 g; b.p. 76–78°C/4 mmHg; $[\alpha]_D^{20}$ = 1.4735, $[\alpha]_D^{20}$ = -18.0°, and 1.6 g of a non-volatile residue.

Esterification of fraction I with *p*-toluenosulfonyl chloride in pyridine afforded 3.8 g of neodihydrocarveol tosylate, m.p. 38.5–40°C. IR of the latter was identical with that of the same compound obtained by another route [9]. Redistillation of fraction II afforded 38.5 g (55.9%) in relation to compound (1) of chromatographically homogeneous nitrile (5), b.p. 76–77°C/4 mmHg; $[\alpha]_D^{20}$ = 1.4773, $[\alpha]_D^{20}$ = -19.0° IR (neat), ν_{max}:1640 cm^{-1} (>C=C<), 2150 cm^{-1} (-C≡N), ^{1}HNMR (CCl_4), δ:0.9 (d,3H,I = 6 Hz (-CH_3 at C_1), 1.6 (s,3H) (⟩C-CH_3) 4.6 (s,2H) (>C=CH_2), 1.0–2.1 (m,8H).

Analysis:

For $C_{11}H_{17}N$ (163.3) calcd.: 80.9% C, 10.5% H, 8,6%N;
found: 80.6% C, 10.7% H, 8.4% N.

4. Reduction of nitrile (5) with LAH

A sample of 8.15 g (0.050 mol) of redistilled fraction II (p. 3) was reduced in the usual manner [22] with 3.0 g (0,071 mol) of LAH in 150 ccm of anhydrous Et_20 to produce 6.8 g (81.6%) of chromatographically homogeneous amine (6), b.p. 79–80°C/3 mmHg; $[\alpha]_D^{20} = 1.4823$, $[\alpha]_D^{20} = -22.4°$ IR (neat), ν_{max}:3400–3300 cm^{-1} ($-NH_2$), 1640 cm^{-1} ($>C=CH_2$), ^{1}HNMR (CCl_4) δ:0.8 (d,3H,I = 6, Hz ($-CH_3$), 0.9 (s,2H disappear at D_2O ($-NH_2$), 1.7 (s,3H) ($\rangle C-CH_3$), 2.7 (m,2H) ($-CH_2$), 4.6 (s,2H) ($>C=CH_2$); 1.0–2.1 (m,9H).

Analysis:

For $C_{11}H_{21}N$ (167.3) calcd.: 78.9% C, 12.7% H, 8,4%N;
found: 79.2% C, 13.0% H, 8.4% N.

Hydrochloride: m.p. 200–201°C $[\alpha]_D^{20} = -300°$ (C=2,C_2H_5OH)

Analysis:

For $C_{11}H_{22}NCl$ (203.8) calcd.: 64.8% C, 10.9% H, 6.9% N, 17.4% Cl;
found: 64.7% C, 11.2% H, 6.8% N, 17.4% Cl.

5. Catalytic reduction of amine (6)

A mixture containing 4.2 g (0.025 mol) amine (6) (p. 5.), 0.42 g Raney nickel and 50 ccm of ethanol was reduced of 80°C under 40 atm of hydrogen presure for 6 hrs. After the reaction the mixture was filtered. The solution was concentrated and distilled under reduced pressure to yield 3.6 g (85.2%) of amine (7), b.p. 79–81°C/2 mmHg; $[\alpha]_D^{20} = 1.4681$; $[\alpha]_D^{20} = -25.1°$ proved to be identical with that of amine obtained by another method [10a]. IR spectra of both compounds were identical. Properties of acetyl derivative of compound (7), m.p. 52–53°C were in agreement with those of acetyl derivative obtained by another method [10a].

6. Hydrolysis of nitrile (5)

A mixture containing 16.3 g (0.100 mol) of redistilled fraction II (p. 3.), 100 ccm of anhydrous ethylene glycol, and 10.0 g (0.180 mol) KOH was refluxed for 24 hrs. The cooled reaction mixture was diluted with a fivefold volume of water and then 100 ccm of *n*-pentane was added. The whole was left standing overnight at 0°C. Then 0.9 g (5.0%) of chromatographically homoge-

neous amide (8), m.p. 186–187°C/acetone-hexane; $[\alpha]_D^{20} = +11.8°$ (C=2, $CHCl_3$) was filtered of IR (KBr), ν_{max}:3400, 3200, 1670, 1620 cm^{-1} (-CO-NH_2), 1640 cm^{-1} (>C=CH_2); ^{1}HNMR ($CDCl_3$), δ:0.9 (d,3H,7I = 7 Hz), (CH_3), 1.7 (s,3H) (⟩C-CH_3), 4.6 (s,2H) (>C=CH_2), 5.5 (m,2H), (⟩C-NH_2) 1.0–1.9 (m,9H).

Analysis:

For $C_{11}H_{19}NO$ (181.3) calcd.: 72.9% C, 10.6% H, 7.7%N;
found: 72.5% C, 10.6% H, 7.6% N.

The remaining filtrate was acidified with 10% H_2SO_4, the pentane layer was separated, and the water solution was extracted with ether (4 × 100 ccm). From the combined and dried extract (anhydrous $MgSO_4$) after filtration and concentration, 12.7 g of crude product, m.p. 86–90°C was obtained. The double crystallization of the latter from *n*-hexane afforded 11.3 d (62.1%) of chromatographically homogeneous acid (9), m.p. 90–91°C; $[\alpha]_D^{20} = +13.7°$ (C=2, CH_3OH); IR (KBr), ν_{max}: 3100, 2700, 1720 cm^{-1} (–COOH), 1640 cm^{-1} (>C=CH_2), ^{1}HNMR (CCl_4) δ:0.9 (d,3H,I = 6 Hz) (–CH_3), 1.7 (s,3H) (⟩C-CH_3), 4.6 (s,2H) (>C=CH_2) 11.9 (s,1H) (–COOH), 1.0-2.1 (m,9H).

Analysis:

For $C_{11}H_{18}O_2$ (182.3) calcd.: 72.5% C, 9.9% H;
found: 72.4% C, 10.3% H.

7. Catalytic reduction of acid (9)

9.1 g (0.050 mol) acid (9) (p. 6.) was reduced of hydrogen with Raney nickel performed in the analogous manner as in p. 5., to afford 8.5 g of crude acide (10). Single crystallization of the latter from aceton-water (1:1) afforded 7.7 g (83.7%) of chromatographically homogeneous acid (10), m.p. 61–61°C; $[\alpha]_D^{20} = +15°$ (C=2 $CHCl_3$) of the latter was identical with that of the same acid obtained by another route [10a].

IR and ^{1}HNMR spectra of both acids were indistinguishable.

8. Cyclization of acid (9) 7-methyl-4-isopropyl-3-oxo-bicyclo-[3.2.1]-octa-non-2 (12)

The mixture containing 4.5 g (0.0247 mol) of acid (9) with 100 ccm of 30% H_2SO_4 was refluxed for 3 hrs. The cooled reaction mixture was extracted with ether (3 × 50 ccm). The combined etheral extracts were shaken with H_2O and next alkalized with Na_2CO_3 to remove nonreactived acid (9). The organic ex-

tract was dried over anhydrous $MgSO_4$, filtered and then concentrated. The crude product was distilled to yield 3.3 g (73,3%) of chromatographically homogeneous lactone (12), b.p. 97°C/2 mmHg; $[\alpha]_D^{20} = 1.475$.

$[\alpha]_D^{20} = -1.2°$: IR (neat), ν_{max}: 2900 cm^{-1} (>CH_2), 1760 cm^{-1} (–C=O), 1385 cm^{-1}, 1370 cm^{-1} (gem–CH_3); ^{1}HNMR (CCl_4), δ: 0.9 (d,3H,I=3 Hz) (-CH_3), 1.0 (d,3H,I=7 Hz) (-CH_3), 2.4 (m,1H) (>C<H, C=O), 1.3–2.2 (m,8H).

Analysis:

For $C_{11}H_{18}O_2$ (182.3) calcd.: 72.5% C, 9.9% H;
found: 72.3% C, 9.7% H.

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STRESZCZENIE

Reakcja (+) tosylanu dihydrokarweolu z KCN w roztworze pirydyny i DMF prowadzi do powstania mieszaniny węglowodorów. Natomiast w roztworze DMSO głównym produktem reakcji jest przestrzennie jednorodny (–)(1S,2R,4S) 1-metylo-4-izopropenylocykloheksylo-2-karbonitryl [(–) neodihydrokarwylokarbonitryl]. Budowę otrzymanych związków ustalono na podstawie danych spektralnych, analizy elementarnej oraz przekształcenia tytułowego związku bez naruszenia konfiguracji absolutnej w znaną (–) (1S,2S,4R) 1-metylo-4-izopropylocykloheksylo-2-metylenoaminę.