STEREOSELECTIVE SYNTHESIS OF N,N'-DIACYL-p-MENTHANE-1,8-DIAMINES

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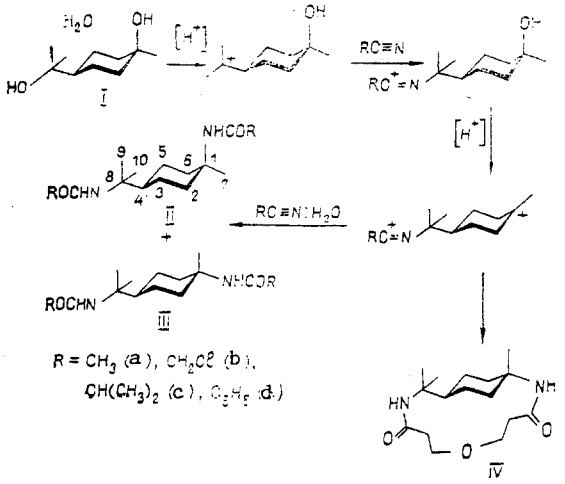
It has been shown that the interaction of terpin hydrate with various nitriles under the conditions of the Ritter reaction takes place stereoselectively and leads to the formation of a mixture of isomeric cis- and trans-N,N'-diacyl-p-methane-1,8-diamines in a ratio of 1:4. The structures of the products have been shown by ^1H and ^{13}C NMR spectroscopy.

In recent years, the reactivity of various terpene derivatives forming key compounds in the synthesis of biologically active substances has been widely studied [1]. Thus, in the literature there is patent information on the synthesis of 1,8-diformamido-p-menthane by the interaction of limonene with hydrogen cyanide in the presence of sulfuric acid with no indication of the stereochemistry of the products synthesized [2]. Attempts to synthesize analogues of this compound were unsuccessful, since the interaction of limonene with other nitriles under identical and analogous conditions led to the formation of monosubstituted products such as N-acyl-p-menth-1-en-8-ylamines [3]. The use of perchloric acid as catalyst in this reaction led to the formation of azabicyclic compounds [4]. The synthesis of 1,8-diacylamines by the interaction of α-terpineol with nitriles also proved to be impossible, since together with the desired products — diamides — a considerable amount of monosubstituted menthanes and also azacyclic compounds was formed [5]. The reaction of dipentene dichloride with acetonitrile led to intensive resinification.

The present investigation was an attempt to synthesize N,N'-diacyl-p-menthane-1,8-diamines using terpin hydrate (I) as the menthane substrate in the Ritter reaction, and also the establishment of the spatial structure of the reaction products.



It has been shown that the interaction of terpin hydrate with various nitriles in the presence of sulfuric acid does actually lead to the formation of mixtures of isomeric cis- and trans-N,N'-diacyl-p-menthane-1,8-diamines (II and III) respectively in a ratio of 1:4. The pure cis-diamines (IIa) and (IId) and trans-diamines (IIIa-d) were isolated by fractional crystallization of the mixtures from acetone.

The structures of the cis- and trans-isomers were ascribed to the amides (II) and (III) on the basis of the results of ^{13}C NMR spectroscopy, which are discussed below. The inter-

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TABLE 1. ^1H NMR Spectra of Compounds (II), (III), and (IV)

Compound	Chemical shifts (δ, ppm) and spin-spin coupling constants (Hz)			
	$C^2-H_a + C^5-H_a$ ($^2J = {}^3J_{a-a}$)	$C^2-H_e + C^5-H_e$ (^2J)	$C^3-H_a + C^5-H_a$ ($^2J = {}^3J_{a-a}$)	$C^3-H_e + C^5-H_e$ (^2J)
IIa	1,48t (12,6)	2,08d (12,6)	1,17q (12,6)	1,60d (12,6)
IIIa	1,50t (13,2)	2,25d (13,2)	1,13q (13,2)	1,56d (13,2)
IIIb	1,68t (12,8)	2,23d (12,8)	1,13q (12,8)	1,56d (12,8)
IIIc	1,56t (12,4)	2,32d (12,4)	1,20q (12,4)	1,49d (12,4)
IId	1,67t (11,6)	2,20d (11,6)	1,28q (11,6)	1,57d (11,6)
IIId	1,72t (12,0)	2,52d (12,0)	1,32q (12,0)	1,63d (12,0)
IV	1,65t (13,0)	2,22d (13,0)	1,13q (13,0)	1,54d (13,0)

Compound	Chemical shifts (δ, ppm) and spin-spin coupling constants (Hz)			
	C^4-H_a ($^3J_{a-a}$)	C^1-CH_3	C^9-CH_3	R
IIa	2,05t(12,6)	1,37s	1,25s	1,90s, 1,91s
IIIa	2,02t(13,2)	1,32s	1,26s	1,92s, 1,95s
IIIb	1,97t(12,8)	1,35s	1,30s	3,91m
IIIc	2,04t(12,4)	1,25s	1,23s	1,05d, 1,07d ($CH(CH_3)_2$), 2,43m ($C\underline{H}(CH_3)_2$)
IId	2,23t(11,6)	1,47s	1,37s	7,56m
IIId	2,26t(12,0)	1,40s	1,40s	7,53m
IV	1,99t(13,0)	1,35s	1,26s	2,40m($COCH_2$), 3,70m(CH_2-O)

action of terpin hydrate with bis(2-cyanoethyl)ethers led to a cyclic diamine – 1,11,11-trimethyl-2,10-diaza-6-oxabicyclo[10.2.2]hexadecane-3,9-dione (IV) – which was purified by vacuum distillation and consisted of the individual trans-isomer.

The structures of all the compounds synthesized were confirmed by the results of IR, mass, and ^1H and ^{13}C NMR spectroscopies. Thus, in the IR spectrum of each of the compounds there were bands at 3300, 3080, and 1560 cm^{-1} corresponding to the vibrations of a N–H bond in a substituted amide, and a band at 1660 cm^{-1} which is characteristic for the vibrations of the C=O bond (amide I). The mass spectrum of each of compounds (II-IV) contains the peak of the molecular ion M^+ with an intensity of 2-6% of the maximum peak in the spectrum.

Details of the PMR spectra of amides (II-IV) are given in Table 1. The assignment of the signals was made on the basis of their multiplicities and the values of the spin–spin coupling constants (SSCCs) and also of a comparison of the values of the chemical shifts with their values for analogues studied previously. Thus, in the PMR spectrum of cis-N,N'-diacetyl-p-menthane-1,8-diamine (IIa) the signals of the methyl groups CH_3-7 (δ 1.37 ppm, s, 3H), CH_3-9 and CH_3-10 (1.25 ppm, s, 6H) were identified. A triplet with a chemical shift of 1.48 ppm (2H, J = 12.6 Hz) was ascribed to the axial protons H-2 and H-6, for which the geminal SSCC (^2J) was approximately equal to the vicinal constant of axial–axial interaction ($^3J_{a-a}$). A signal with a chemical shift of 2.08 ppm (d, 2H) was ascribed to the equatorial H-2 and H-6 protons (^2J = 12.6 Hz), a quartet with a chemical shift of 1.17 ppm (2H, 12.6 Hz) to the axial H-3 and H-5 protons; a doublet with a chemical shift of 1.60 ppm (2H, J = 12.6 Hz) to the equatorial protons at the same atoms, and a triplet at 2.05 ppm (1H, J = 12.6 Hz) to the H-4 proton.

The PMR spectra of the trans-isomer of N,N'-diacetyl-p-methane-1,8-diamine (IIIa) had an analogous form: a singlet with a chemical shift of 1.32 ppm (3H) was ascribed to the protons of the CH_3-7 methyl group; a signal with a chemical shift of 1.26 ppm to the CH_3-9 and CH_3-10 methyl groups (s, 6H); a triplet with a chemical shift of 1.50 ppm (2H, J = 13.2 Hz) to the H-2 and H-6 axial protons; a doublet at 2.25 ppm (2H, ^2J = 13.2 Hz) to the equatorial protons at the same atoms; a quartet with a chemical shift of 1.13 ppm (2H, J = 13.2 Hz) to the H-3 and H-5 axial protons; a signal with a chemical shift of 1.56 ppm (d, 2H, ^2J = 13.2 Hz) to the equatorial protons at the same atoms, and, finally, a triplet with a chemical shift of 2.02 ppm (1H, J_{a-a} = 13.2 Hz) to the H-4 proton.

As can be seen from the facts given, in the spectra of both isomeric amides the signals of the protons at the C^4 atoms had the form of triplets with SSCC values corresponding to axial–axial interactions. Consequently, in both cases the H-4 proton had the axial orienta-

TABLE 2. ^{13}C NMR Spectra of Compounds (II), (III), and (IV)

Compound	Chemical shifts (δ, ppm) and multiplicities of the signals of the ^{13}C nuclei								
	C^1	C^3+C^6	C^3+C^5	C^4	C^6	C^1-CH_3	C^6-CH_3	C=O	R
IIa	54,8s	38,2t	24,7t	45,4d	57,6s	21,9q	24,1q	172,7s	24,9q
IIIb	53,8s	37,4t	23,6t	44,8d	57,2s	28,0q	23,8q	172,0s, 172,5s	24,4q
IIb*	54,9s	37,3t	24,1t	45,2d	57,8s	21,4q	24,4q	171,4s	44,1t
IIIb	54,3s	37,0t	23,3t	44,7d	57,7s	27,6q	24,4q	171,7s	44,0t
IIIc	53,8s	37,6t	23,8t	45,0d	57,2s	28,1q	24,7q	179,2s, 179,6s	36,7d, 20,1q, 20,3q
IId	54,0s	37,4t	23,2t	44,2d	57,0s	21,6q	24,5q	167,1s, 169,9s	126,8d, 127,4d, 128,5d, 135,8s
IIId	54,8s	37,5t	24,6t	45,1d	58,2s	28,0q	24,8q	170,2s, 170,6s	128,1d, 128,6d 129,4d, 135,0s
IV	54,0s	36,7t	23,0t	44,6d	57,5s	27,9q	24,4q	172,6s	59,2d, 27,0t

*Compound (IIb) could not be isolated in the pure form. The ^{13}C NMR spectrum of this compound was obtained by recording the spectrum of a mixture enriched with the cis-isomer, after the deduction of the signals of compound (IIIb).

tion, and the $C(CH_3)_2NHCOCH_3$ group the equatorial orientation. Thus, the isomeric diamides (II) and (III) differed from one another only by the spatial orientation of the substituent at the C^1 atom. Because of this, the values of the chemical shifts of the signals of the corresponding protons in the cis- and trans-isomeric diamides (II) and (III) had very close values, and only the signals of the equatorial H-2 and H-6 protons differed, by approximately 0.2 ppm, in connection with the change in the 1,2-nonbound interaction with the amide group at the C^1 atom, which has the axial orientation in the cis-isomer and the equatorial orientation in the trans-isomer.

Conclusions concerning the spatial structure of the isomeric 1,8-diacyl-p-menthane-1,8-diamines (II and III) isolated were drawn on the basis of the results of ^{13}C NMR spectroscopy. Thus, it is known from the literature that the signal of a methyl group at the C^1 atom of a methane ring having the equatorial orientation is shifted upfield by approximately 6 ppm as compared with an axially oriented group [6]. In our case, the shift of the methyl group at the C^1 atom for compound (IIa) was 21.9 ppm, and for compound (IIIa) it was 28.0 ppm (Table 2). Consequently, compound (IIa) was the cis-isomer with the equatorial orientation of the methyl group and the axial orientation of the amide group, and compound (IIIa) had to be ascribed the structure of the trans-isomer.

The predominant formation during the reaction of the trans-isomer of the diamide (~80% in the mixture) agrees well with considerations relative to the stabilities of products (II) and (III). Thus, it is obvious that the formation of the trans-isomer with the equatorial orientation of the two senior substituents should take place preferentially in comparison with the formation of the cis-isomer with the axial orientation of the amide group at the C^1 atom.

It must be mentioned that on the interaction of terpin hydrate with nitriles no information of monosubstituted menthene derivatives was observed, and the diamides (II) and (III) were the only reaction products. This result of the transformation is apparently due to differences in the reactivity of the hydroxy group at the C^1 atom of terpin hydrate in comparison with that of the double bond in limonene or α-terpineol.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were taken on a Bruker WM-360 spectrometer with resonance frequencies of 360.134 MHz for ^1H and 90.56 MHz for ^{13}C. The concentration of the solutions was 10% in deuteromethanol. Chemical shifts were determined relative to an internal standard – HMDS. IR spectra were recorded on a UR-20 spectrometer. Mass spectra were obtained on a Varian MAT-311 instrument.

The course of the reaction was followed and the purity of the products synthesized was determined by the GLC method on a Chrom-5 chromatograph with a glass column (2 × 2000 mm) filled with Chromaton N-AW-DMCS (0.16-0.20) impregnated with Apiezon L.

The initial terpin hydrate (technical product) was purified by extraction with hexane in a Soxhlet apparatus, mp 116°C (according to the literature [7], 116-117°C).

The Ritter reaction was performed by the following procedures.

1. A mixture of 5 g (26 mmoles) of terpin hydrate and 200 mmoles of the nitrile was cooled in an ice bath, and 6 ml (105 mmoles) of concentrated H_2SO_4 was added slowly dropwise. Then the temperature was allowed to rise gradually to that of the room, and the mixture was stirred until the reaction was complete (from 36 to 72 h). After this, it was poured into an excess of strongly cooled aqueous ammonia, the mixture was extracted with an excess of chloroform, and the extract was dried with anhydrous magnesium sulfate. Compounds (II), (III), and (IV) were practically insoluble in ether and sparingly soluble in chloroform, and therefore their extraction required a large volume of chloroform. The product obtained after the sovlent had been distilled off was purified by recrystallization.

2. A mixture of 5 g (26 mmoles) of terpin hydrate, 65 mmoles of a nitrile, and 7 ml dibutyl ether was cooled in an ice bath, and sulfuric acid was slowly added. Then the experiment was performed as described above.

The N,N'-diacetyl-p-menthane-1,8-diamines (IIa + IIIa) were obtained by procedure 1 with a yield of 4.2 g (64%). The pure compounds (IIa) and (IIIa) were obtained by the fractional crystallization of the mixture from acetone.

cis-N,N-'Diacetyl-p-menthane-1,8-diamine (IIa). mp 244-246°C. IR spectrum, λ_{max}^{KBr}, cm^{-1}: 3300, 3080 (N–H), 2970, 2950, 2880 (C–H), 1660 (C=O, amide I), 1560 (N–H). Mass spectrum, m/z: 254 (M^+), 210, 196, 195, 180, 166, 156, 155, 152, 137, 122, 121, 110, 108, 99, 98, 82, 81, 70, 69, 58.

trans-N,N'-Diacetyl-p-menthane-1,8-diamine (IIIa). mp 190°C. IR spectrum, λ_{max}^{KBr}, cm^{-1}: 3320, 3290, 3080 (N–H), 2970, 2950, 2880 (C–H), 1660 (C=O), amide (I), 1560 N–H). Mass spectrum, m/z: 254 (M^+), 210, 196, 195, 180, 166, 156, 152, 137, 122, 121, 110, 108, 99, 98, 82, 81, 70, 69, 58.

N,N'-Di(chloroacetyl)-p-menthane-1,8-diamines (IIb + IIIb) were obtained by procedure 1 with a yield of 4.2 g (50%). The pure trans-N,N'-di(chloroacetyl)-p-menthane-1,8-diamine (IIIb) was obtained by fractional crystallization of the mixture from acetone, with mp 138°C. IR spectrum, λ_{max}^{KBr}, cm^{-1}: 3300, 3090 (N–H), 2980, 2960, 2890 (C–H), 1670 (C=O, amide I), 1560 (N–H). Mass spectrum, m/z: 323 (M^+), 309, 307, 287, 279, 273, 231, 229, 214, 200, 191, 190, 189, 154, 146, 140, 136, 135, 121, 107, 100, 97, 81, 77, 70, 69, 58.

The N,N'-diisobutyryl-p-menthane-1,8-diamines (IIc + IIIc) were obtained by procedure 2 with a yield of 4.8 g (68%). In an attempt to obtain the desired products by procedure 1 (without dibutyl ether, excess of isobutyronitrile), intensive hydrolysis of the nitrile took place and the isolation of the desired product was complicated by the presence of a large amount of the primary isobutyramide in the reaction mixture. Pure trans-N,N'-diisobutyryl-p-menthane-1,8-diamine (IIc) was isolated by recrystallizing the mixture of (IIc + IIIc) from acetone, with mp 178-180°C. IR spectrum, λ_{max}^{KBr}, cm^{-1}: 3300, 3090 (N–H), 2975, 2950, 2880 (C–H), 1650 (C=O, amide I), 1560 (N–H). Mass spectrum, m/z: 310 (M^+), 267, 239, 223, 208, 183, 152, 136, 128, 121, 108, 99, 88, 58.

The N,N'-dibenzoyl-p-methane-1,8-diamines (IId + IIId) were obtained by procedure 2 with a yield of 5.9 g (60%). The use of procedure 1 was undesirable for the same reasons as in the preceding case. The pure cis- and trans-diamines (IId) and (IIId) were isolated by fractional crystallization of the mixture from acetone.

cis-N,N'-Dibenzoyl-p-methane-1,8-diamine (IId). mp 233-235°C. IR spectrum, λ_{max}^{KBr}, cm^{-1}: 3340, 3070 (N–H), 3040 (aromatic C–H), 2960, 2900, 2870 (aliphatic C–H), 1660 (C=O, amide I), 1580 (aromatic C=C), 1560 (N–H), 1500 (aromatic C=C). Mass spectrum, m/z: 378 (M^+), 363, 335, 273, 257, 242, 228, 217, 188, 174, 163, 162, 152, 148, 136, 122, 121, 106, 105, 93, 79, 77, 58.

trans-N,N'-Dibenzoyl-p-methane-1,8-diamine (IIId). mp 152-154°C. IR spectrum, λ_{max}^{KBr}, cm^{-1}: 3330, 3080 (N–H), 3030 (aromatic C–H), 2960, 2910, 2870 (aliphatic C–H), 1650 (C=O, amide I), 1590 (aromatic C=C), 1550 (N–H), 1510 (aromatic C=C). Mass spectrum, m/z: 378 (M^+), 363, 335, 273, 257, 242, 228, 217, 188, 174, 163, 162, 152, 148, 136, 122, 121, 106, 105, 93, 79, 77, 58.

1,11,11-Trimethyl-2,10-diaza-6-oxabicyclo[10.2.2]hexadecane-3,9-dione (IV) was obtained by procedure 1 and was purified by vacuum distillation. bp 180-185°C (4 mm Hg). Yield 3.1 g (40%). IR spectrum, λ_{max}^{KBr}, cm^{-1}: 3320, 3080 (N–H), 2980, 2950, 2880 (C–H), 1660 (C=O, amide I), 1560 (N–H), 1120 (C–O–C). Mass spectrum, m/z: 296 (M^+), 225, 207, 192, 136, 121, 112, 109, 92, 87, 83, 70, 58.

SUMMARY

The interaction of terpin hydrate with various nitriles under the conditions of the Ritter reaction leads stereoselectively to the formation of mixtures of isomeric cis- and trans-N,N'-diacyl-p-menthane-1,8-diamines in a ratio of 1:4. The structures of the products have been shown by ^1H and ^{13}C NMR spectroscopy.

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OXIDATION OF TRITERPENES DERIVED FROM 18-LUPENE AND 18,19-SECOLUPANE WITH RUTHENIUM TETROXIDE BY AN IMPROVED PROCEDURE

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A convenient preparative procedure for the oxidation with ruthenium tetroxide of 18-lupene derivatives to 18,19-secolupane-18,19-dione derivatives in an ethyl acetate–water system has been developed. It has been found that 3β,28-diacetoxy-18,19-secolupane-18,19-dione can be obtained from its 19-(ethylene acetal) or 19-oxime by reaction with ruthenium tetroxide.

The problem of the rational use of betulin (3β,28-dihdyroxy-20(29)-lupene), a widely available triterpenoid of the lupane series is still far from exhausted [1]. One of the interesting routes of the chemical transformation of triterpenes of this series is their conversion into derivatives of tetracyclic triterpenes of the baccharane (18,19-secolupane) series [2]. Triterpenes with the skeleton of 18,19-secolupane have been proposed as an intermediate link between the dammarane series and the lupane and shionane series in the scheme of biogenetic transformations of triterpenes [3]. They have been synthesized from lupeol [4] and have been obtained in the skeletal rearrangement of the so-called baccharis oxide (hence their name – baccharanes), isolated from the roots of Baccharis halimifolia L. [5]. Only two examples of the isolation of native baccharanes from plants are known [6].

In this paper we give results relating to the development of a preparative method for synthesizing baccharane derivatives via the ruthenium tetroxide oxidation of a betulin isomerization product.

Betulin diacetate (I) was converted in dry benzene into 3β,28-diacetoxy-18-lupene (II) by the action of a mixture of the reagents HBr, Ac_2O, and AcOH in the optimum molar ratio (1:1.3:4.7) according to [7]. We raised the concentration of (I) in the reaction mixture 10- to 15-fold in comparison with [7], which made this procedure more suitable for preparative purposes (by making it cheaper and decreasing the total amount of wastes), in spite of the fact that the reaction time increased by a factor of 1.5-3, and the yield of product (II) fell from 87 to 74-80%.

The action of NaOH on a solution of (II) in EtOH–C_6H_6 gave 3β,28-dihydroxy-18-lupene (III) from which, by reactions with succinic and glutaric anhydride in pyridine the bis(hydrogen succinate) and bis(hydrogen glutarate) of 3β,28-dihydroxy-18-lupene (IV and VI) were synthesized, these being characterized in the form of their methyl esters (V) and (VII).

The procedure for the ruthenium tetroxide oxidation of 18-lupene derivatives was developed with compound (II) as an example. We first reproduced the known procedure [2] for oxidizing (II) to a baccharane derivative – 3β,28-diacetoxy-18,19-secolupane-18,19-dione (VIII). The reaction was performed in a H_2O–CCl_4 two-phase system with a catalytic amount of $RuO_2 \cdot xH_2O$ from which, in the aqueous phase under the action of $NaIO_4$ the RuO_4 that had oxidized the substrate in the CCL_4 phase was regenerated and was again converted into RuO_2. This procedure for the oxidation of organic compounds by RuO_4 has been used most frequently [8]. However, to complete the reaction even with 2 mmoles of (II) required vigorous stirring for 20 h [2]. The reason for the prolonged course of oxidation by

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