MANNICH REACTION IN A NUMBER OF SIX-MEMBERED HETEROCYCLIC γ-KETONES. XI*. AMINOMETHYLATION OF 2,2,5-TRIMETHYL-4-OXOTETRAHYDROPYRAN AND 2,2,5-TRIMETHYL-4-OXOTETRAHYDROTHIAPYRAN AND REDUCTION OF THE RESULTING AMINO KETONES

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The structural specificity of the aminomethylation of 2,2,5-trimethyl-substituted 4-oxotetrahydropyran and 4-oxotetrahydrothiapyran was investigated by a study of the structures of the resulting amino ketones by PMR spectroscopy and mass spectrometry. It is shown that the reaction is directed exclusively to the tertiary carbon atom adjacent to the carbonyl group and leads to the corresponding 5-(dimethylaminomethyl)-substituted derivatives. Reduction of the products with lithium aluminum hydride and aluminum isopropoxide in both cases also gives only one spatial isomer of the amino alcohols, the structure of which was established by means of the PMR and IR spectra.

In a continuation of our study of the orientation of the Mannich reaction in a series of variously methyl-substitued saturated six-membered heterocyclic γ-ketones we carried out the aminomethylation of 2,2,5-trimethyl-4-oxotetrahydropyran (I) [2] and 2,2,5-trimethyl-4-oxotetrahydrothiapyran (II) [3] by means of dimethylamine hydrochloride and 30% formalin in aqueous methanol.

In agreement with the data from preceding papers (for example, [4]), the aminomethylation of ketones I and II occurs by substitution of the axial tertiary hydrogen atom adjacent to the carbonyl group in the 5 position. In both cases only one structural isomer of the amino ketones — 2,2,5-trimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran (III, in 61% yield) and 2,2,5-trimethyl-5-dimethylaminomethyl-4-oxotetrahydrothiapyran (IV, in 56% yield) — is formed.

The structures of amino ketones III and IV are confirmed by the presence in their PMR spectra of singlets of protons of the 5-CH_3 group at 0.96 and 1.12 ppm† and also by the presence in the mass spectra of these compounds of peaks with m/e 98 corresponding to the characteristic $CH_2=C(CH_3)CH=\overset{+}{N}(CH_3)_2$ fragmention.

The intense peaks with m/e 58 are related to the $CH_2=\overset{+}{N}(CH_3)_2$ immonium ion. The molecular ion peaks correspond to the molecular weights of the compounds.‡

*See [1] for communication X.

†The numerical values here and subsequently are indicated in accordance with the order of numbering of the compounds.

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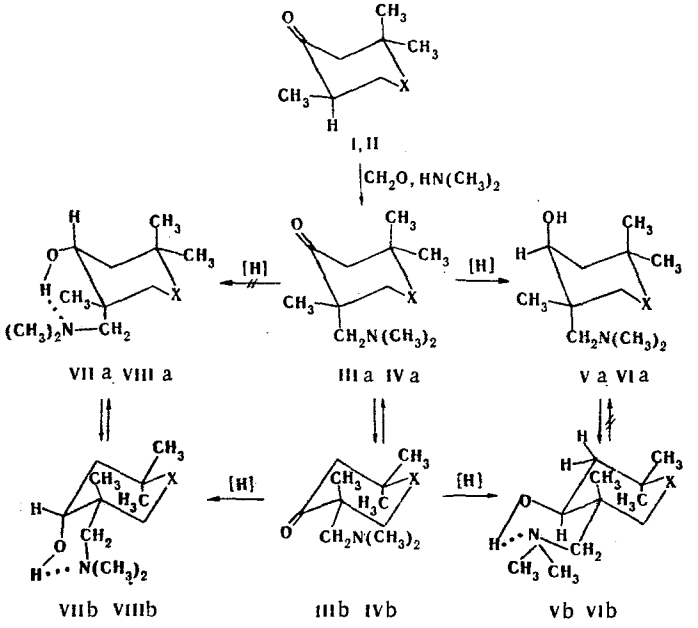
Only one spatial isomer of the amino alcohols — 2,2,5-trimethyl-5-dimethylaminomethyl-4-hydroxytetrahydropyran (V) and 2,2,5-trimethyl-5-dimethylaminomethyl-4-hydroxytetrahydrothiapyran (VI) — is also obtained in each case in the reduction of amino ketone III and IV with both lithium aluminum hydride and aluminum isopropoxide. The resulting amino alcohols have identical three-dimensional structures, as follows from their IR and PMR spectra. The IR spectra of both amino alcohols contain strong absorption bands of stretching vibrations of a hydroxyl group tied up in an intramolecular hydrogen bond with the amino group (3270 and 3200 cm^{-1}) and weak absorption bands of a free hydroxyl group (3605 and 3610 cm^{-1}).



I, III, V, VII X = O; II, IV, VI, VIII X = S

The signals of the 4-H proton (δ 3.63 and 3.40 ppm) in the PMR spectra of the amino alcohols are split because of coupling with the protons of the adjacent methylene group. The J_{4a3a} and J_{4a3e} values of 11 Hz and 5 Hz, respectively, constitute evidence that the conformational equilibrium in solutions of amino alcohols V and VI is shifted to favor one of the conformers. According to the these data, the 4-H protons should be axially oriented, and both amino alcohols consequently are equatorial alcohols. In addition, their PMR spectra contain singlets of protons of the 5-CH_3 group at δ 1.02 and 1.12 ppm and singlets of protons of axial and equatorial 2-CH_3 groups at δ 1.10-1.14, 1.15, 1.17 ppm, and protons of a dimethylamino group at δ 2.28 ppm. Because of the absence of a second epimeric amino alcohol, it is extremely difficult to draw a definite conclusion regarding the three-dimensional structure of the molecules of the amino alcohols obtained. However, on the basis of the available spectral data and an analogy in the structures of the amino alcohols described in a previous communication [1], it can be assumed that the investigated amino alcohols most likely have a trans configuration relative to the aminomethyl and hydroxyl groups and a preferred conformation, in solution, with a diequatorial orientation of these substituents (Vb, VIb).

EXPERIMENTAL

The mass spectra of amino ketones III and IV were obtained with an MKh-1303 spectrometer at an ionizing-electron energy of 70 eV. The PMR spectra of carbon tetrachloride solutions of amino ketones III and IV and amino alcohols V and VI were recorded with an RS-60 spectrometer with tetramethylsilane as the internal standard. The IR spectra of carbon tetrachloride solutions of the compounds ($5 \cdot 10^{-3}$ M) were recorded with a UR-10 spectrometer with an LiF prism. Thin-layer chromatography (TLC) of the compound was carried out on activity II aluminum oxide in a petroleum ether—ether system in the ratio indicated in parentheses after the R_f values. The hydrochlorides were obtained by passing dry hydrogen chloride into a solution of the base in anhydrous ether and were recrystallized from alcohol—acetone (1:3).

2,2,5-Trimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran (III). A mixture of 28.4 g (0.2 mole) of 4-oxotetrahydropyran I [bp 65-66° (5 mm)], 25 g (0.3 mole) of dimethylamine hydrochloride, 37 ml (0.4 mole) of 30% formalin, and 15 ml of methanol acidified with five drops of concentrated hydrochloric acid was heated at 100° for 8 h, after which the methanol was removed by vacuum distillation, and the neutral substances were extracted with ether. Workup of the extract yielded 2 g (7%) of starting pyranone I. The aqueous solution was made alkaline with 40% NaOH solution, and the base was extracted with ether. The extract was dried with $MgSO_4$, and the ether was removed by vacuum distillation to give 24.4 g (61%) of amino ketone III with bp 66-69° (0.5 mm), d_4^{20} 0.9649, n_D^{20} 1.4556, and R_f 0.60 (1:2). Mass spectrum: m/e 28, 56, 58, 84, 98, and 199 (M^+). PMR spectrum: δ 0.96 (s, 5-CH_3), 1.13 (s,2-CH_3), 1.17 (s, 2-CH_3), and 2.12 ppm [s, $N(CH_3)_2$]. Found: C 66.4; 66.5; H 11.0; 10.9; N 7.4; 7.2%; MR_D 56.23. $C_{11}H_{21}NO_2$. Calculated: C 66.3; H 10.6; N 7.0%; MR_D 56.35. The hydrochloride had mp 181-182°. Found: Cl 15.5, 15.4%. $C_{11}H_{21}NO_2$. Calculated: Cl 15.0%.

2,2,5-Trimethyl-5-dimethylaminomethyl-4-oxotetrahydrothiapyran (IV). A mixture of 23.7 g (0.15 mole) of 4-oxotetrahydrothiapyran II [bp 65-66° (2 mm)], 16 g (0.2 mole) of dimethylamine hydrochloride, 28 ml (0.3 mole) of 30% formalin, and 15 ml of methanol acidified with five drops of concentrated hydrochloric acid was heated at 100° for 12 h, after which it was worked up as in the preceding experiment to give 2 g (9%) of unchanged starting thiapyranone II and 18.2 g (56%) of amino ketone IV with mp 82-85° (0.5 mm), d_4^{20} 1.0077, n_D^{20} 1.4948, and R_f 0.68 (1:1). Mass spectrum, m/e: 28, 56, 58, 84, 98, 155, and 215 (M^+). PMR spectrum, δ: 1.12 (s, 5-CH_3), 1.28 (s, 2-CH_3), 1.30 (s, 2-CH_3), and 2.22 [s, $N(CH_3)_2$]. Found: N 6.6; 6.5; S 14.6; 14.8%. MR_D 62.38. $C_{11}H_{21}NOS$. Calculated: N 6.5; S 14.9%; MR_D 62.50. The hydrochloride had mp 189-190°. Found: Cl 14.0; 14.2%. $C_{11}H_{21}NOS \cdot HCl$. Calculated: Cl 14.1%.

2,2,5-Trimethyl-5-dimethylaminomethyl-4-hydroxytetrahydropyran (V). A) An 11.8-g (0.05 mole) sample of the hydrochloride of amino ketone III was added in small portions with cooling (to −30°) and stirring to a suspension of 1.5 g (0.038 mole) of lithium aluminum hydride in 200 ml of anhydrous ether, after which the mixture was heated at 38-40° for 2 h. It was then cooled to −20° and hydrolyzed with 6 ml of water and 1.5 ml of 15% NaOH solution. The solid material was separated and washed on the filter with ether. The ether solution was dried with $MgSO_4$, the ether was removed by distillation, and the residue was vacuum distilled to give 7.9 g (78%) of amino alcohol V with bp 60-63° (0.2 mm) and R_f 0.28 (1:4). IR spectrum: 3270 (OH_{bond}) integral intensity $4.86 \cdot 10^4$ $cm^{-2} \cdot mole^{-1} \cdot liter$; 3605 cm^{-1} (OH_{free}). Found: C 66.2; 66.2; H 11.5; 11.6; N 7.0; 7.1%. $C_{11}H_{23}NO_2$. Calculated: C 65.6; H 11.5; N 7.0%. The hydrochloride had mp 178-180°. Found: Cl 14.8; 14.7%. $C_{11}H_{23}NO_2 \cdot HCl$. Calculated: Cl 14.9%.

B) A mixture of 10 g (0.05 mole) of amino ketone III and 20.4 g (0.1 mole) of aluminum isopropoxide in 150 ml of isopropyl alcohol was refluxed for 4 h, after which it was cooled and hydrolyzed with 50 ml of 50% NaOH solution. The organic layer was separated, acidified to pH ∿ 2 with hydrochloric acid, and vacuum evaporated to dryness. The residue was dissolved in water, and the solution was saturated with potassium carbonate. The base was extracted with ether, and the ether extract was dried with $MgSO_4$. Vacuum distillation gave 4.6 g (46%) of amino alcohol V with bp 62-66° (0.2 mm) and R_f 0.28; the product was identical to that described in experiment A.

2,2,5-Trimethyl-5-dimethylaminomethyl-4-hydroxytetrahydrothiapyran (VI). A) A 12.6-g (0.05 mole) sample of the hydrochloride of amino ketone IV was reduced as described in the preceding experiment with 1.5 g (0.038 mole) of lithium aluminum hydride in 200 ml of anhydrous ether. Workup of the reaction mixture gave 8.9 g (82%) of amino alcohol VI with bp 82-84° (0.2 mm) and R_f 0.45 (1:3). IR spectrum: 3200 (OH_{bond}) (integral intensity $5.4 \cdot 10^4$ $cm^{-2} \cdot mole^{-1} \cdot liter$) and 3610 cm^{-1} (OH_{free}). Found: N 6.4; 6.3; S 14.6; 14.6%. $C_{11}H_{23}NOS$. Calculated: N 6.6; S 14.8%. The hydrochloride had mp 174-176°. Found: Cl 14.0; 13.8%. $C_{11}H_{23}NOS \cdot HCl$. Calculated: Cl 14.0%.

B) Reduction of 10.8 g (0.05 mole) of amino ketone IV with 20.4 g (0.1 mole) of aluminum isopropoxide in 200 ml of isopropyl alcohol as described above gave 5.1 g (48%) of amino alcohol VI with mp 81-84° (0.2 mm) and R_f 0.45.

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CONFORMATIONAL ANALYSIS OF THE STEREOISOMERS OF 3-METHYL-2-OXO-2-THIABICYCLO[4.4.0]DECANE

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The conditions for the separation of the stereoisomeric sulfones and sulfoxides of 3-methyl-2-thiabicyclo[4.4.0]decane were found by means of capillary gas—liquid chromatography, and the relative thermodynamic stabilities of the latter were determined. The configuration of the stereoisomeric sulfoxides was established on the basis of oxidation data, the characteristics of the physicochemical properties, and the Kerr effect.

In developing the stereochemistry of thiabicycloalkanes that model petroleum sulfides and their derivatives [1] we obtained sulfones from four of the stereoisomers of 3-methyl-2-thiabicyclo[4.4.0]decane [2] and sulfoxides from two of them and established the configuration of the latter.

For uniformity in the nomenclature of the thiabicycloalkanes we will subsequently use the IUPAC nomenclature for bicyclic hydrocarbons with a condensed system of rings. The three-dimensional orientation of the substituents is most conveniently examined with respect to the hydrogen atom attached to the angular carbon atom with which numbering is commenced. In this case it is most illustrative to compare the three-dimensional orientation of the angular hydrogen atom and the hydrogen atom attached to the tertiary carbon atom bonded to the alkyl substituent. The cis configuration of the alkyl group is assigned to this isomer when the latter have identical orientations.

TABLE 1. Stereoisomers of 3-Methyl-2,2-dioxo-thiabicyclo-[4.4.0]decane

Compound	Configuration	mp, °C (solvent)	Retention time, min
III	cis, trans	102,5—103,5[a]	31,23
IV	cis, trans	—[b]	31,35
V	trans, trans	69—71[a]	34,57
VI	trans, cis	92—94[c]	39,75

[a] From ethanol. [b] n_D^{20} 1.5098. [c] From methanol.

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