MANICH REACTION IN A NUMBER OF SIX-MEMBERED
HETEROCYCLIC γ-KETONES. XT*. 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 spec-
trometry. 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-(di-
methylaminomethyl)-substituted derivatives. Reduction of the products with lith-
ium aluminum hydride and aluminum isopropanoxide 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-substituted 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-CH₃ group at 0.96 and 1.12 ppm and also by the pre-
sence in the mass spectra of these compounds of peaks with m/e 98 corresponding to the char-
acteristic CH₃ = C(CH₃)CH=N(CH₃)₂ fragmentation.

The intense peaks with m/e 58 are related to the CH₂ = N(CH₃)₂ immonium ion. The molec-
ular 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).

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 J₄a₃a and J₄a₃e 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 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-CH₃ group at δ 1.02 and 1.12 ppm and singlets of protons of axial and equatorial 2-CH₃ 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 (5×10⁻³ 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 Rf 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).