MANNICH REACTION IN A NUMBER OF SIX-MEMBERED HETEROCYCLIC γ-KETONES

IX.* SYNTHESIS AND STRUCTURE OF 2,2-DIMETHYL-5-AMINOMETHYL-4-OXO- AND 2,2-DIMETHYL-4-PHENYL-5-AMINOMETHYL-4-HYDROXY-TETRAHYDROPYRANS

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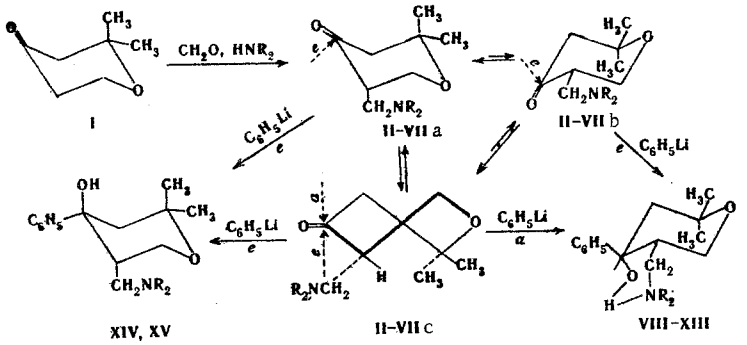
Aminomethylation of 2,2-dimethyl-4-oxotetrahydropyran gave a number of its aminomethyl derivatives, which were converted to tertiary γ-amino alcohols by phenylation. The individual structural and geometrical isomers were isolated, and their structures were established by mass spectrometry and PMR and IR spectroscopy.

The synthesis of β-amino ketones and γ-amino alcohols of the tetrahydropyran series was undertaken in order to obtain esters designated for pharmacological study of their anesthetizing activity.

Aminomethylation of 2,2-dimethyl-4-oxotetrahydropyran (I) [2] with 30% formalin and secondary amine hydrochlorides gave 2,2-dimethyl-5-aminomethyl-4-oxotetrahydropyrans (II-VII).



II, VIII, XIV NR_2=$N(C_2H_5)_2$; III, IX NR_2=$N(C_3H_7)_2$; IV, X NR_2=$N(C_4H_9)_2$; V, XI NR_2=$N(CH_2)_5$; VI, XII, XV NR_2=$N(CH_2)_6$; VII, XIII NR_2=$N(CH_2CH_2)_2O$

Analysis of the reaction products by means of thin-layer chromatography (TLC) showed that only one structural isomer of the corresponding amino ketone (II-VII) is formed in all cases (Table 1).

The structures of amino ketones II-VII were confirmed by their PMR spectra and mass spectra (in the case of II and VI). The mass spectra contain peaks of characteristic $CH_2=CHCH_2\overset{+}{N}(C_2H_5)_2$ fragment ions (m/e 113) in the case of amino ketone II and of $CH_2=CHCH_2\overset{+}{N}(CH_2)_6$ fragment ions (m/e 139) in the case of amino ketone VI and peaks with m/e 86 and 112 of $CH_2=\overset{+}{N}(C_2H_5)_2$ and $CH_2=\overset{+}{N}(CH_2)_6$ immonium ions, along with molecular ion peaks with m/e 213 and 239.

Fragments with alternative structures of the amino ketones are absent in the mass spectra. Thus it was established that the aminomethylation of 2,2-dimethyl-substituted ketone I, regardless of the character

*See [1] for communication VIII.

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TABLE 1. 2,2-Dimethyl-5-aminomethyl-4-oxotetrahydropyrans (II-VII)

Compound	bp, °C (mm)	R_f[a]	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Empirical formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %[b]	Hydrochloride, mp, °C[c]
II	105—108 (2)	0,78	0,9695	1,4650	60,82	61,02	$C_{12}H_{23}NO_2$	67,5 67,4	10,8 11,1	6,47 6,77	67,6	10,9	6,6	60 (85)	129—130
III	112—116 (1)	0,87	0,9441	1,4604	70,08	70,35	$C_{14}H_{27}NO_2$	69,4 69,5	11,2 11,4	6,1 6,0	69,7	11,3	5,8	58	128—129
IV	80—85 (0,2)	0,90	0,9204	1,4580	79,87	79,59	$C_{16}H_{31}NO_2$	71,6 71,8	11,8 11,8	5,2 5,4	71,3	11,6	5,2	54	127—128
V	101—105 (1,5)	0,75	1,0107	1,4846	63,85	63,50	$C_{13}H_{23}NO_2$	69,2 69,4	10,3 10,4	6,1 6,4	69,3	10,3	6,2	68 (86)	228—230
VI	96—102 (3)	0,94	1,0131	1,4895	68,23	68,15	$C_{14}H_{25}NO_2$	70,2 70,2	10,4 10,5	5,8 5,8	70,2	10,5	5,8	61 (86)	191—192
VII	117—121 (3)	0,79	1,0714	1,4839	60,70	60,62	$C_{12}H_{21}NO_3$	63,5 63,3	9,4 9,5	5,9 5,8	63,4	9,3	6,2	51 (80)	149—150

[a] From acetone–benzene (1:5).
[b] The yield of hydrochloride during isolation of the amino ketones in the form of a salt is given in parentheses.
[c] From alcohol–acetone (1:3). The composition was confirmed by analysis for chlorine.

TABLE 2. 2,2-Dimethyl-4-phenyl-5-aminomethyl-4-hydroxytetrahydropyrans (VIII-XIII)

Compound	mp, °C	R_f[a]	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	ν_{OH}, cm^{-1}	Yield of isomer mix., %	Hydrochloride, mp, °C[b]
VIII	59,5—60,5[c]	0,63	$C_{18}H_{29}NO_2$	74,0 74,0	10,2 9,9	4,8 5,0	74,1	10,0	4,8	3170	93	212—213
IX	44—46[d]	0,75	$C_{20}H_{33}NO_2$	75,1 75,3	10,5 10,7	4,3 4,4	75,2	10,4	4,4	3165	82	193—194
X	36—37[c]	0,79	$C_{22}H_{37}NO_2$	75,9 76,0	10,4 10,7	4,2 4,3	76,0	10,7	4,0	3205	88	203—204
XI	78—79[e]	0,65	$C_{19}H_{22}NO_2$	75,0 75,3	9,6 9,4	4,2 4,3	75,2	9,6	4,5	3160	75	232—233
XII	81—82[d]	0,66	$C_{20}H_{31}NO_2$	75,4 75,5	9,9 9,9	4,3 4,4	75,1	10,5	4,4	3160	84	239—240
XIII	129—130[e]	0,41	$C_{18}H_{27}NO_3$	70,6 70,5	8,6 8,4	4,5 4,3	70,8	8,9	4,6	3210	87	252—253

[a] From petroleum ether–ether (1:3). The R_f values of the amino alcohols epimeric to VIII-XII are 0.46, 0.54, 0.55, 0.39, and 0.35.
[b] From alcohol–acetone (1:3). The composition of the hydrochlorides were confirmed by analysis for chlorine.
[c] From hexane.
[d] From heptane.
[e] From heptane–ethanol.

of the entering aminomethyl group, proceeds structurally specifically with the participation only of the methylene group opposite the methyl substituents in the heterocyclic ring. As we have previously shown (for example, see [1,3]), the orientation of the Mannich reaction depends exclusively on the structure of the starting ketone, namely, on the number and position of alkyl substituents in the ring.

The PMR spectra of amino ketones II and VI contain two singlet resonance signals (δ 1.12 and 1.18 ppm) of the protons of the axial and equatorial methyl groups in the 2 position and two quartets of the axial (δ 3.50 ppm) and equatorial (δ 4.10 ppm) 6-H protons. The values of the vicinal constants of spin–spin coupling of the 6-H protons with the 5-H vicinal protons (J_{trans} = 6.5-7.0 Hz and J_{cis} = 4.5-5.0 Hz with $J_{6Ha, 6He}$ = 12 Hz) constitute evidence that amino ketones II-VII in carbon tetrachloride and benzene either exist primarily in the flexible (twist) form IIc-VIIc) or that they exist in a conformational equilibrium (a⇌b), inasmuch as the trans-vicinal constants have an averaged value. In this case, in the determination of J [3] it is probably also necessary to take into account the change in the dihedral angles and the distortion of the chair form in the tetrahydral pyranone as compared with the ideal cyclohexane system due to the trigonal carbon atom of the carbonyl group and the oxygen heteroatom.

Amino ketones II-VII were converted to the corresponding 2,2-dimethyl-4-phenyl-5-aminomethyl-4-hydroxytetrahydropyrans (VIII-XIII) by phenylation with phenyllithium; mixture of two stereoisomeric amino alcohols in which one of the isomers predominates are formed in this case. A single amino alcohol (XIII) is formed only from amino ketone VII. The individual geometrical isomers of amino alcohols VIII-XIII (Table 2) were obtained by crystallization of the bases. In two cases we were able to isolate the second three-dimensional isomers of amino alcohols XIV and XV by means of preparative TLC of the mixture of bases on aluminum oxide (the percentage of these isomers in the mixture does not exceed 5%).

A conclusion regarding the three-dimensional structures of amino alcohols VII-XV was drawn on the basis of the IR spectra and the general principles of conformational analysis. Intense absorption bands in the region of the stretching vibrations of a hydroxyl group included in an intramolecular hydrogen bond with the nitrogen atom of an amino group (3160-3210 cm^{-1}) are observed in the IR spectra of dilute solutions of amino alcohols VIII-XIII. It is completely evident that the formation of an intramolecular hydrogen bond in cyclic γ-amino alcohols between a vicinal hydroxyl group and an aminomethyl group is possible only for a trans-diequatorial or cis-equatorial–axial orientation of these groups relative to one another. At the same time, the phenyl substituent in the 4 position, which has a large effective volume, should occupy primarily the equatorial position [4-7]. Thus these facts speak in favor of the existence of amino alcohols VIII-XIII with a cis configuration of the hydroxyl and aminomethyl groups and in a primary conformation, in solution, with an equatorial orientation of both the phenyl and aminomethyl groups and an axial orientation of the hydroxyl group. The tertiary γ-amino alcohols previously obtained by phenylation of other heterocyclic β-amino ketones [8] have the same three-dimensional structure. On the other hand, the IR spectra of amino alcohols XIV and XV contain exclusively the absorption bands of a free hydroxyl group (3620 and 3610 cm^{-1}, respectively), which constitute evidence for the only possible conformation of these amino alcohols, in solution, with a trans-diaxial orientation of the hydroxyl and aminomethyl groups.

It is known that steric factors have a substantial effect on the stereochemistry of the reactions of organometallic synthesis. Thus equatorial attack of the reagent predominates in all of the previously investigated examples of the reaction of phenyllithium with cyclic ketones, and the axial epimer of the alcohol is always present in preponderant quantities in the reaction products [4,5]. Phenylation of sterically hindered amino ketones II-VII especially should occur via attack by the nucleophilic reagents on the carbonyl group from the unhindered equatorial region, inasmuch as approach of the reagent from the axial side is blocked by the meta-axial methyl substituent in the 2 position. There are a sufficient number of examples of this in the literature (for example, see [9, 10].

On the basis of the material stated above, it can be assumed that amino alcohols VIII-XIII are formed from conformers of amino ketones IIb-VIIb, whereas amino alcohols XIV, XV may be formed from conformers of amino ketones IIa-VIIa. The fact that tertiary amino alcohols are obtained in predominant amounts in the VIII-XIII conformation but not the XIV and XV conformation can be explained by the fact that the former are thermodynamically more stable as a result of the formation of an intramolecular hydrogen bond and, in addition, an intermediate cyclic complex of the chelate type may arise during their formation from the conformers of amino ketones IIb-VIIb through the metal atom of the reagent, the nitrogen atom of the amino group, and the oxygen atom of the carbonyl group. In the case of the formation of amino alcohols VIII-XV from the flexible form of amino ketones IIc-VIIc, pseudoaxial attack of the carbonyl group, which leads to amino alcohols VIII-XIII, proves to be preferable to pseudoequatorial attack, inasmuch as the

steric hindrance of the methyl groups in the 2 position becomes minimal as a consequence of their symmetrical orientation in the ring, and the ease of approach of the reagent to the carbonyl group is determined by the adjacent polar aminomethyl group. The insignificant participation of the conformers of amino ketones IIa-VIIa in the reaction is also probably a consequence of the fact that equatorial attack is shielded by the adjacent axially oriented aminomethyl group.

EXPERIMENTAL

The PMR spectra of solutions of amino ketones II and VI in carbon tetrachloride and benzene (the spectra of solutions of the compounds in these solvents are identical) were recorded with a Chart S-100A (100 MHz) spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra of amino ketones II and VI were obtained with an MKh-1303 spectrometer with an ionizing-electron energy of 30-40 eV. The IR spectra of solutions of amino alcohols VIII-XV in carbon tetrachloride ($5 \cdot 10^{-3}$ M) were recorded with a UR-20 spectrometer. Thin-layer chromatography was acidified to pH ~ 2 with concentrated layer of activity II aluminum oxide in acetone–benzene (1:5) for amino ketones II-VII and in petroleum ether–ether (1:3) for amino alcohols VIII-XV. The hydrochloride salts were obtained by addition of a saturated solution of dry hydrogen chloride in anhydrous ether to a solution of the base in ether.

2,2-Dimethyl-5-diethylaminomethyl-4-oxotetrahydropyran (II). A) A mixture of 12.8 g (0.1 mole) of oxotetrahydropyran I, 13 g (0.12 mole) of diethylamine hydrochloride, 18.5 ml (0.2 mole) of 30% formalin, and 10 ml of methanol was acidified to pH 2 with concentrated hydrochloric acid, and the mixture was heated at 80-85° for 8 h. The methanol was then removed by vacuum distillation, and the residue was extracted with ether. Workup of the extract yielded 1.2 g (10%) of unchanged pyranone I. The acidic aqueous solution was saturated with potassium carbonate, and the liberated base was extracted repeatedly with ether. The ether extract was dried with magnesium sulfate, and the ether was removed by vacuum distillation to give 12.7 g (60%) of amino ketone II (Table 1). Mass spectrum m/e 28, 56, 73, 86, 113, 127, 129, 185, 213 (M^+).

B) The reaction was carried out similarly, but after separation of starting pyranone I, the acidic aqueous solution was vacuum evaporated to dryness, and the crystalline residue was washed with acetone. It was then removed by filtration and dried to give 21.2 g (85%) of the hydrochloride of amino ketone II. The base was isolated from the salt by treatment with 40% NaOH solution and subsequent extraction with ether and vacuum distillation.

Amino ketones III-VII (Table 1) were obtained by method A, while amino ketones V-VII were also obtained by method B. Mass spectrum of amino ketone VI: m/e 28, 56, 99, 112, 127, 139, 211, 239 (M^+).

2,2-Dimethyl-4-phenyl-5-diethylaminomethyl-4-hydroxytetrahydro-pyrans (VIII, XIV). A 12.5-g (0.05 mole) sample of the hydrochloride of amino ketone II was added in a nitrogen atmosphere with stirring and cooling (−10°) to phenyllithium, [prepared from 2.1 g (0.3 g-atom) of lithium and 24 g (0.15 mole) of bromobenzene in 250 ml of anhydrous ether], after which the mixture was refluxed for 2 h, cooled to −10°, and acidified to pH 2 with dilute (1:1) hydrochloric acid. The organic layer was separated, and the aqueous layer was washed with ether and saturated with potassium carbonate. The bases were extracted with ether, and the extract was dried with $MgSO_4$ and filtered. The residue obtained after removal of the ether by distillation began to crystalize to give 15.1 g (93%) of a mixture of stereoisomers VIII and XIV. Individual amino alcohol VIII was obtained by crystallization of the mixture of bases of amino alcohols VIII and XIV from hexane (Table 2). Amino alcohol XIV, present in no more than 5% amounts, was isolated from the mixture of bases VIII and XIV by preparative TLC. Amino alcohol XIV had mp 86-87° (from hexane) and R_f 0.46. IR spectrum: 3620 cm^{-1} (OH). The hydrochloride had mp 207-208°. Found: Cl 11.4%. $C_{18}H_{29}NO_2 \cdot HCl$. Calculated: Cl 10.8%. A mixture of the hydrochlorides of amino alcohols VIII and XIV melt at 190-192°.

2,2-Dimethyl-4-phenyl-5-hexamethyleneiminomethyl-4-hydroxytetrahydropyrans XII and XV. As described above, 6.7 g (84%) of a mixture of stereoisomers XII and XV was obtained from phenyllithium [prepared from 1.1 g (0.15 g-atom) of lithium and 12 g (0.075 mole) of bromobenzene in 150 ml of anhydrous ether] and 7 g (0.025 mole) of the hydrochloride of amino ketone VI. Amino alcohol XII was obtained by crystallization of the mixture of bases from heptane (Table 2). Amino alcohol XV, which was isolated from the mixture by preparative TLC, had mp 86.5-87° (from heptane) and R_f 0.35. IR spectrum: 3610 cm^{-1} (OH). The hydrochloride had mp 217-218° (from ethyl acetate–methanol). Found: Cl 9.8; N 3.8%. $C_{20}H_{31}NO_2 \cdot HCl$. Calculated: Cl 10.0; N 3.9%.

Amino alcohols IX-XI and XII (Table 2) were obtained by the same method.

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