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

VIII.* STRUCTURES OF THE PRODUCTS OF AMINOMETHYLATION OF 2,2-DIMETHYL-4-OXOTETRAHYDROPYRAN, 2,2-DIMETHYL-4-OXOTETRAHYDROTHIOPYRAN, AND 1,2,2-TRIMETHYL-4-OXOPIPERIDINE

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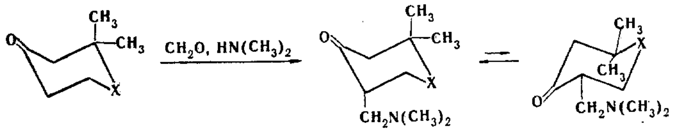
It was established by PMR spectroscopy and mass spectrometry that the aminomethylation of 2,2-dimethyl-substituted oxygen-, sulfur-, and nitrogen-containing six-membered cyclic γ-ketones gives the corresponding 5-aminomethyl derivatives.

In our preceding communications [1, 2] we showed that the orientation of the Mannich reaction in a series of saturated cyclic ketones depends to a marked degree on the number of alkyl substituents and their position relative to the carbonyl group.

In order to ascertain the effect on the specificity of the Mannich reaction of two methyl substituents in the β position relative to the carbonyl group as well as the character of the heteroatom (O, S, N) in the ring, we studied the structures of the products of aminomethylation of 2,2-dimethyl-4-oxotetrahydropyran (I) [3], 2,2-dimethyl-4-oxotetrahydrothiopyran (II) [4], and 1,2,2-trimethyl-4-oxopiperidine (III) [5]. Ketones I and II have been previously subjected to aminomethylation, but the structures of the amino ketones obtained have not been established [6].

The aminomethylation of ketones I-III was accomplished both in acidic and alkaline media by means of a 33% aqueous solution of dimethylamine or its hydrochloride and 30% formalin. In both cases the reaction proceeds with the participation of only one of the two methylene groups adjacent to the carbonyl group on the side of the heteroring opposite the methyl substituents and gives, respectively, 2,2-dimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran (IV) (71% yield in acidic media and 44% yield in alkaline media), 2,2-dimethyl-5-dimethylaminomethyl-4-oxotetrahydrothiopyran (V) (68% yield in acidic media), and 1,2,2-trimethyl-5-dimethylaminomethyl-4-oxopiperidine (VI) (61% yield in alkaline media).

It is well known [7, 8] that the pH of the medium has a large effect on the rate and yields of the Mannich reaction. The aminomethylation of ketones of neutral character (tetrahydropyranones and tetrahydrothiopyranones) proceeds well both in acidic and alkaline media. In the case of acid catalysis, heating of the



I-III IV-VI a IV-VI

I, IV X=O; II, V X=S; III, VI X=NCH$_3$

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*See [1] for communication VII.

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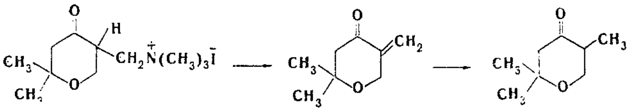
mixture of reagents at 80-100° for 8-10 h is necessary to obtain high yields of the reaction product. At the same time, the aminomethylation of piperidiones can be accomplished in high yields only in alkaline media. However, in alkaline media the reaction with any of the investigated ketones proceeds very vigorously and is accompanied by pronounced warming up of the reaction mixtures, and this leads to resinification and a decrease in the yield of the desired product.

The structures of amino ketones IV-VI were established by mass spectrometry and PMR spectroscopy. The mass spectra of the investigated compounds contain peaks of the structure of the fragment ion characteristic for them with m/e 84 $CH_2{=}CH{-}CH{=}\overset{+}{N}(CH_3)_2$, and peaks with m/e 58 of the immonium ion $CH_2{=}\overset{+}{N}(CH_3)_2$. Fragments of alternative structure are absent.

The PMR spectra of amino ketones IV-VI at δ 1.12-1.17 and 1.18-1.23 ppm contain two singlet resonance signals of the protons of the axial and equatorial methyl groups in the 2 position and two quartets of the axial (3.40-3.55 ppm) and equatorial (4.07-4.23 ppm) 6-H protons. It is not possible to determine the signal of the 5-H proton, inasmuch as the signals of the 3-H protons are superimposed on it at 2.30-2.69 ppm. The spin-spin coupling constants (SSCC) of the 6-H_a and 6-H_e protons with the vicinal 5-H proton, obtained from their signals by direct measurement ($J_{6\text{-}H_a,5\text{-}H_e} = 7$ Hz and $J_{6\text{-}H_a,5\text{-}H_e} = 5$ Hz, as compared with $J_{6\text{-}H_a,6\text{-}H_e} = 12$ Hz) and calculated by the standard method (7.01 and 4.99 Hz) [9], constitute evidence that amino ketones IV-VI exist in carbon tetrachloride solution in conformational equilibrium (a⇌b) or in the flexible twist form.

An additional proof of the structure of Mannich bases IV-VI can be obtained by exhaustive Hofmann methylation [10] through cleavage of their quaternary ammonium salts. Thus, for example, the methiodide of amino ketone IV was converted to the known 2,2-trimethyl-4-oxotetrahydropyran (VII) [11] by reductive deamination.



VII

EXPERIMENTAL

The mass spectra of amino ketones IV-VI were obtained with an MKh-1303 spectrometer at an ionizing-electron energy of 30-40 eV. The PMR spectra of solutions of IV-VI in CCl_4 were recorded with RF-60 and Varian HA-100 spectrometers with tetramethylsilane as the internal standard. Chromatography of the compounds in a thin layer of loose activity II Al_2O_3 was carried out with petroleum ether-ether in the ratio indicated in parentheses after the R_f values.

2,2-Dimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran (IV). A) A mixture of 12.8 g (0.1 mole) of oxotetrahydropyran I, 12 g (0.15 mole) of dimethylamine hydrochloride, 18.5 ml (0.02 mole) of 30% formalin, and 10 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 distillation, and the aqueous residue was treated with ether. The ether extract was worked up to give 1.4 g (11%) of unchanged pyranone I. The acidic aqueous solution was made alkaline with 40% NaOH solution, and the base was extracted repeatedly with ether. The extract was dried with $MgSO_4$, the ether was removed by distillation, and the residue was vacuum-fractionated to give 13.2 g (71%) of the amino ketone [6] with bp 77-81° (2 mm), n_D^{20} 1.4654, and R_f 0.51 (1:2). Mass spectrum: m/e 58, 84, 98, 125, and 185 (M^+). The methoidide had mp 208-209° (from alcohol). Found: I 39.0, 39.1%. $C_{11}H_{22}INO_2$. Calculated: I 38.8%. The hydrochloride had mp 143-144° [from alcohol-acetone (1:3)]. Found: Cl 16.1; 16.2%. $C_{10}H_{19}NO_2 \cdot HCl$. Calculated: Cl 16.0%. Aminoketone IV, isolated from the salt by treatment with aqueous 40% NaOH and extraction with ether, began to crystallize after removal of the ether by distillation to give a product with mp 74-75° (from hexane).

In an attempt to aminomethylate tetrahydropyranone I by means of dimethylamine hydrochloride and paraformaldehyde with methanol and ethanol as the solvents we recovered unchanged pyranone I even upon prolonged refluxing of the solutions.

B) A 38.4-g (0.3 mole) sample of pyranone I was added dropwise in the course of 20 min to a cooled (to 0-5°) mixture of 62 ml (0.4 mole) of 33% dimethylamine and 37 ml (0.4 mole) of 30% formalin, after which the mixture was stirred at 20° for 3 h. It was then acidified to pH $\sim$ 2 with hydrochloric acid, and the neutral substances were extracted with ether. Workup of the extract yielded 10.5 g (27%) of pyranone I. An aqueous solution of the base was worked up in the usual manner, and vacuum distillation gave 24.8 g (44%) of aminopyranone IV with bp 90-95° (3 mm), n_D^{20} 1.4605, and R_f 0.51 (1 : 2). The hydrochloride had mp 143-144°, and no melting-point depression was observed for a mixture of it with the salt obtained in experiment A.

2,2-Dimethyl-5-dimethylaminomethyl-4-oxotetrahydrothiopyran (V). In analogy with experiment A, 20.5 g (68%) of aminoketone V [6], with bp 73-75° (1 mm), and 2 g (10%) of starting thiopyranone II were obtained from 21.6 g (0.15 mole) of oxotetrahydrothiopyran II, 16 g (0.2 mole) of dimethylamine hydrochloride, and 28 ml (0.3 mole) of 30% formalin in the presence of 15 ml of methanol and five drops of concentrated hydrochloric acid. The reaction product began to crystallize completely to give a product with mp 45-46° (from hexane) and R_f 0.64 (1 : 1). Mass spectrum: m/e 58, 84, 101, and 201 (M^+). The methiodide had mp 241-242° (from alcohol – acetone). Found: I 37.3; 37.4%. $C_{11}H_{22}INOS$. Calculated: I 37.1%. The hydrochloride had mp 148-149° (from alcohol – acetone). Found: Cl 14.7; 14.6; N 6.2; 6.1%. $C_{10}H_{19}NOS \cdot HCl$. Calculated: Cl 14.9; N 5.9%.

1,2,2-Trimethyl-5-dimethylaminomethyl-4-oxopiperidine (VI). A solution of 10 g (0.12 mole) of dimethylamine hydrochloride in 14 ml (0.15 mole) of 30% formalin was added dropwise with cooling and stirring to 14.1 g (0.1 mole) of oxopiperidine III at such a rate that the temperature of the mixture did not rise above 5°. The mixture was then held at 0° for 1 h, after which it was saturated with potassium carbonate and extracted with ether. The extract was dried with $MgSO_4$, the ether was removed by distillation, and the residue was vacuum-distilled to give 12.2 g (61%) of amino ketone VI with bp 96-103° (3 mm), d_4^{20} 0.9496, and n_D^{20} 1.4745. Found: C 66.8; 66.9; H 11.5; 11.4; N 13.8; 13.8%; MR_D 58.66. $C_{11}H_{22}N_2O$. Calculated: C 66.6; H 11.2; N 14.1%; MR_D 58.36. Mass spectrum: m/e 58, 84, 138, and 198 (M^+). The dimethiodide had mp 192-194° (from alcohol). Found: I 52.8; 52.9; N 6.5; 6.3%. $C_{13}H_{28}I_2N_2O$. Calculated: I 52.6; N 5.8%.

The reaction did not take place in acidic media even on prolonged refluxing of the solution of hydrochlorides of piperidione III and dimethylamine in formalin.

2,2,5-Trimethyl-4-oxotetrahydropyran (VII). A 20-g sample of 50% NaOH solution was added to a solution of 5 g of the methiodide of amino ketone IV in 50 ml of water, after which 6 g of powdered nickel – aluminum alloy was added in small portions with stirring and cooling (0°). The mixture was then stirred at 20° for another 2 h, after which it was acidified to pH $\sim$ 2 with HCl, and the reaction product was extracted repeatedly with ether. The extract was dried with $MgSO_4$, the ether was removed, and the residue was vacuum-distilled to give 1.3 g (61%) of pyranone VII [10] with bp 64-67° (12 mm) and n_D^{20} 1.4450. The 2,4-dinitrophenylhydrazone had mp 149-150° (from alcohol). No melting-point depression was observed for a mixture of this product with a genuine sample.

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