HERBICIDAL DERIVATIVES OF HYDROXYLAMINE

XXXIII.* REACTIONS OF O-(N'-METHYLCARBAMIDOMETHYL)-N-CARBOISOPROPOXY-N-PHENYLHYDROXYLAMINE

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The prototropic transformation of O-(N'-methylcarbamidomethyl)-N-carboisopropoxy-N-phenylhydroxylamine in the presence of sodium ethoxide to form isopropyl phenylcarbamate, N-phenyl-N'-methylurea, and glyoxylic acid derivatives was studied. A similar reaction with 2-phenyl-4-methyl-1,2,4-oxadiazine-3,5-dione is accompanied by ring contraction and the formation of 1-phenyl-3-methyl-5-hydroxyhydantoin.

N-Carboalkoxy-N-arylhydroxylamines (I), under the comparatively mild conditions of heating at 80-120 deg C, undergo various reactions of radical cleavage and rearrangement with migration of the hydroxyl group to the aromatic ring and also have oxidizing action [2]. These properties are associated with the presence in I of a free hydroxyl group on the nitrogen atom, since the corresponding O-acetyl derivatives of I are completely stable even at and above 180 deg [3]. The stabilizing effect of a carbonyl group attached to the oxygen atom in the hydroxylamine grouping is weakened to a significant degree if there is a methylene group between them. Thus O-carbamidomethyl-N-carboalkoxy-N-arylhydroxylamines (II) are cleaved under mild conditions in the presence of alkali and alcohol to form the corresponding esters of arylcarbamic acid, glyoxylic acid derivatives, and 2-aryl-1,2,4-oxadiazine-3,5-diones, which are stable in alkaline solutions [3].

In continuing these investigations we have studied the reaction of O-(N'-methylcarbamidomethyl)-N-carboisopropoxy-N-phenylhydroxylamine (III) with alcoholic sodium ethoxide. As in the case of II, isopropylphenylcarbamate (IV) and N-methylglyoxylamide (V) could be isolated in the reaction products. However, in contrast to II, not even traces of the expected cyclization product – 2-phenyl-4-methyl-1,2,4-oxadiazine-3,5-dione (VI) – could be detected in this case, but a high yield of N-phenyl-N'-methylurea (VII) was isolated in place of it, and the presence of ethyl glyoxylate (VIII) was qualitatively demonstrated. The production of VII can be explained by the formation of VI, which is unstable under the reaction conditions. In fact, VII was isolated in almost quantitative yield by the reaction of VI, obtained by the methylation of 2-phenyl-1,2,4-oxadiazine-3,5-dione [3], with an alcohol solution of an equimolar amount of sodium ethoxide with subsequent heating of the reaction mixture. However, in the presence of catalytic or equimolecular amounts of sodium ethoxide in the cold, the reaction could be stopped at the stage involving the formation of the primary product, 1-phenyl-3-methyl-5-hydroxyhydantoin (IX). The latter is an extremely unstable compound which readily undergoes hydrolysis or alcoholysis under the influence of hot water or alcohol, respectively, to form VII and the corresponding glyoxylic acid derivative.

The composition and structure of IX were confirmed by measurement of the molecular weight (198 ± 8) by a cryoscopic method, by its ability to give a silver-mirror reaction and a sodium salt (X), and by the formation of 1-phenyl-3-methyl-5-methoxyhydantoin (XI) on methylation of IX with methyl iodide or dimethyl sulfate in the presence of potassium carbonate.

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[*] See [1] for communication XXXII.

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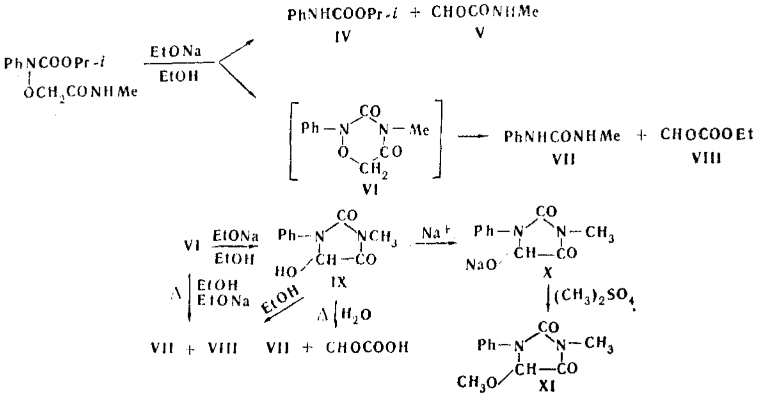
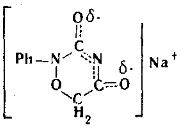


Additional confirmation of the structure of IX and XI was obtained by means of the IR and PMR spectra. In contrast to the IR spectra of X and XI, the IR spectrum of IX (obtained from a KBr pellet from 3100 to 3800 cm^{-1}) contains an intense band at 3375 cm^{-1}, which, from its position and structure, corresponds to the frequency of a hydroxyl group participating in a hydrogen bond. The spectra of IX contain two intense bands at 1700 and 1783 cm^{-1} which can be assigned to the symmetrical and asymmetrical valence vibrations of the two carbonyl groups in the five-membered ring [4, 5].

The width of the ν_{CO} bands, the shift of the low-frequency ν_{CO} band by 17 cm^{-1} to low frequencies as compared with the analogous band in the spectrum of XI, and the sharp increase in the ν_{OH} frequency in dilute solutions of IX in CCl_4 indicate the presence of strong hydrogen bonds in crystals of IX. The IR spectra of X and XI are close at 3100-3800 cm^{-1} and 1700-1800 cm^{-1}. The PMR spectrum* of IX in deuteroacetone consists of lines at 2.98 and 5.68 ppm and a group of lines in the region characteristic for the spectrum of phenyl protons. From the position of the lines and the ratio of their intensities [6], it can be assumed that the line at 2.98 ppm is related to the protons of the $N-CH_3$ group, while the line at 5.68 ppm is related to the protons of the CH(OH) group. The PMR spectrum of a solution of XI in CCl_4 contains signals at 2.95 ppm ($N-CH_3$), 3.23 ppm ($O-CH_3$), 5.32 ppm ($CH-OCH_3$), and a multiplet in the region characteristic for the spectrum of phenyl protons. The intensities of these lines are in a ratio of 3:3:1:5, respectively.

The instability of VI in the presence of alcohol and base differs sharply from 2-aryl-1,2,4-oxadiazine-3,5-diones, which do not contain substituents in the 4-position and are completely stable under these conditions. This difference is probably due to the conversion of the latter, in the presence of sodium ethoxide, to the stable anion (XII)



The recyclization of VI to IX under the influence of alcoholic sodium ethoxide proceeds under mild conditions and does not have close analogies in the cyclic derivatives of hydroxylamine. The reaction studied by us may be a new preparative method for the preparation of 5-hydroxyhydantoin derivatives – an important class of physiologically active compounds – and will subsequently be studied in greater detail for other examples.

EXPERIMENTAL

Reaction of III with Alcoholic Sodium Ethoxide. A solution of 1.78 g (0.067 mole) of III in 10 ml of ethanol was added dropwise with cooling to 10-15 deg to a solution of sodium ethoxide prepared from 0.154 g (0.067 g-atom) of sodium metal and 10 ml of absolute ethanol. The mixture was stirred at 10-15 deg for 30 min, and 20 ml of water was added after vacuum evaporation of the alcohol. The insoluble residue was filtered to give 0.3 g (25%) of IV with mp 87-88 deg (from hexane) which was not depressed by an authentic sample of IV. Found %: C 67.2; H 7.4; N 7.9. $C_{10}H_{13}NO_2$. Calc. %: C 67.1; H 7.3; N 7.8.

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* The PMR spectrum was obtained with a DA-60L spectrometer. Hexamethyldisiloxane was used as the internal standard. The δ scale is used in this paper.

The aqueous, alkaline mother liquor was cooled and acidified with hydrochloric acid to pH 6-6.5 and extracted with four 25-ml aliquots of ether. The ether extracts were dried over calcined magnesium sulfate, and the ether was distilled to give 0.65 g (64.7%) of VII with mp 154-155 deg (from benzene) (mp 152 deg [7]) and R_f 0.41 [hexane – acetone (4:3)] from thin-layer chromatography on a fixed layer. Found %: C 63.9; H 5.9; N 18.6. $C_8H_{10}N_2O$. Calc. %: C 64.0; H 6.03; N 18.6. The melting point was not depressed by an authentic sample of VII.

To detect V and VIII, 1 ml of the reaction mixture was added to 5 ml of an ammoniacal solution of silver nitrate. The solution darkened after several minutes, and a "silver mirror" formed on the walls of the test tube after standing for several hours.

Reaction of VI with Alcoholic Sodium Ethoxide. A) A solution of 0.25 g (0.0012 mole) of VI in the minimum amount of alcohol was added dropwise with cooling at 10-15 deg to a solution of sodium ethoxide obtained from 0.03 g (0.0013 g-atom) of sodium metal and 5 ml of absolute ethanol, and the mixture was stirred at this temperature for 1 h. The alcohol was then removed by vacuum distillation, and 30 ml of dry ether saturated with hydrogen chloride was added to the residue. The resulting white precipitate of VII was filtered, washed with water, and air-dried to give 0.17 g (94.5%) of a product with mp 152 deg. The ether was distilled from the filtrate, and the residue (0.11 g) was dissolved in carbon tetrachloride. Chromatography of this solution revealed a white spot with the same R_f value as VIII. The reaction mixture gave a "silver-mirror" reaction similar to that in the above experiment.

B) A solution of 0.30 g (0.0014 mole) of VI in 4 ml of ethanol was mixed with a solution of catalytic or equimolecular amounts of sodium ethoxide in 10 ml of absolute ethanol and stirred at –10 deg for 30 min. The mixture was then neutralized with concentrated hydrochloric acid, and the precipitate that formed on cooling the mixture to 0 deg was filtered. The alcohol was removed from the mother liquor by vacuum distillation, and the minimum amount of water was added to the residue. The solution was cooled to 0 deg, and the resulting precipitate was filtered and added to the first precipitate to give 0.13 g (89%) of IX with mp 181-182 deg (from benzene) and R_f 0.57 [hexane – acetone (4:3)]. Found %: C 58.2; H 5.0; N 13.6. $C_{10}H_{10}N_2O_3$. Calc. %: C 58.2; H 4.9; N 13.6. Compound IX gave a distinct "silver-mirror" reaction at 60-70 deg.

1-Phenyl-3-methyl-5-methoxyhydantoin (XI). A) Potassium carbonate [0.5 g (0.0036 mole)] was added to a solution of 0.46 g (0.0022 mole) of IX in 10 ml of dry acetone, and 0.56 g (0.0038 mole) of methyl iodide was added dropwise to this suspension at 22-24 deg. The mixture was stirred for ~ 8 h, the precipitate (KI) was filtered, and the acetone was removed by vacuum distillation with a water aspirator. The oily residue (0.49 g) was a mixture of starting IX and XI. The latter was isolated by extraction with hot hexane to give 0.19 g (40%) of a product with mp 65 deg and R_f 0.62 [hexane – acetone (4:3)]. Found %: C 60.0; H 5.4; N 12.7. $C_{11}H_{12}N_2O_3$. Calc. %: C 60.0; H 5.4; N 12.7.

B) Under similar conditions, 0.13 g (81.7%) of XI with mp 64-65 deg was obtained from 0.21 g (0.001 mole) of IX in 5 ml of acetone, 0.25 g (0.002 mole) of dimethyl sulfate, and 0.25 g (0.0018 mole) of potassium carbonate for a reaction time of 16 h.

Sodium Salt of 1-Phenyl-3-methyl-5-hydroxyhydantoin (X). Compound IX [0.23 g (0.001 mole)] was stirred for 30 min with an equimolecular amount of sodium ethoxide in 3 ml of ethanol at 15 deg. The resulting precipitate was filtered, washed with alcohol and acetone, and air-dried to give 0.2 g (88.7%) of a product that melted above 200 deg. Found %: N 11.9. $C_{10}H_9N_2O_3Na$. Calc. %: N 12.2.

In this study, thin-layer chromatography on a fixed layer of KSK silica gel (~ 0.06 mm) was used. A universal developer was used to detect the spots.

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