REACTION OF α,α-DIMETHYL-γ-(1-PHENYL-3-METHYL-4-PYRAZOLYL)-$\Delta^{\beta,\gamma}$-BUTENOLIDE WITH PRIMARY AMINES AND AMMONIA

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The conditions for the formation of amides of 4-keto acids, 2-oxo-5-hydroxypyrrolidines, 2-oxo-2,3-dihydropyrroles, or 2-oxo-5-aminotetrahydrofurans by reaction of a $\Delta^{\beta,\gamma}$-butenolide with primary amines were determined. The reaction with primary aliphatic amines – benzylamine and methylamine – in ethanol gives 2-oxo-5-hydroxypyrrolidines, while reaction with benzylamine in benzene gives the amide of a 4-keto acid. 2-Oxo-5-anilinotetrahydrofuran is formed in the reaction with aniline.

The reaction of $\Delta^{\beta,\gamma}$-butenolides with primary amines is of considerable interest in view of the possibility of the formation of an entire series of reaction products, in particular amides of γ-keto acids and hydroxylactams, which are ring-chain isomers. In the most recent and most detailed studies [1, 2] it is shown that hydroxylactams are formed only in the reaction with methylamine, while amides of γ-keto acids are formed with other amines. In the case of α- or β-monosubstituted γ-aryl-$\Delta^{\beta,\gamma}$-butenolides the double bond migrates with the formation of $\Delta^{\alpha,\beta}$-butenolides and the products of their reaction with amines [1]. α,α-Disubstituted γ-aryl-$\Delta^{\beta,\gamma}$-butenolides react with aliphatic primary amines to give only hydroxylactams, but they do not react with aromatic amines [1].

For the first time we were able to synthesize [3] α,α-disubstituted $\Delta^{\beta,\gamma}$-butenolides with a heterocyclic nitrogen-containing substituent of aromatic nature in the γ-position. In connection with what was stated above, it seemed of interest to study the reaction of α,α-dimethyl-γ-(1-phenyl-3-methyl-4-pyrazolyl)-$\Delta^{\beta,\gamma}$-butenolide (I) with primary amines and ammonia.

In the present research we made a detailed study of the reaction of butenolide I with benzylamine. The results make it possible to rigorously determine the conditions for the formation of any of the three (IIa-IVa) reaction products. Compound I does not react with benzylamine at room temperature in ethanol or benzene. At the boiling points of the solvents, the structures of the reaction products depend on the polarity of the solvents: 2,2-dimethyl-4-keto-4-(1-phenyl-3-methyl-4-pyrazolyl)butanoic acid benzylamide (IIa) is formed in benzene, while 1-benzyl-2-oxo-3,3-dimethyl-5-hydroxy-5-(1-phenyl-3-methyl-4-pyrazolyl)pyrrolidine (IIIa) is formed in ethanol. Both amide IIa and hydroxylactam IIIa give the same product – 1-benzyl-2-oxo-3,3-dimethyl-5-(1-phenyl-3-methyl-4-pyrazolyl)-2,3-dihydropyrrole (IVa) – on refluxing in acetic anhydride.

The structures of IIa-IVa were confirmed by the IR spectra. The forms of the absorption curves corresponding to ν_{NH} in IIa and ν_{OH} in IIIa follow the regularities previously observed [1, 4, 5] for compounds of these types.

Hydroxylactam IIIb was obtained from butenolide I and methylamine in ethanol at room temperature, while a mixture of IIIb and 2,2-dimethyl-4-keto-4-(1-phenyl-3-methyl-4-pyrazolyl)butanoic acid methylamide (IIb), which could not be separated preparatively, was obtained in benzene.

Compound I does not react with dry ammonia in benzene.

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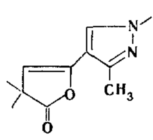
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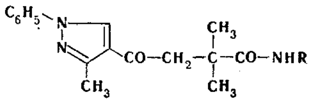
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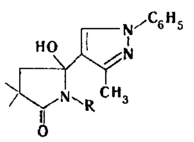
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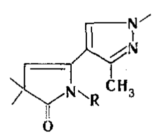
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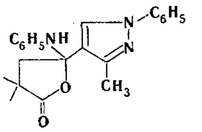
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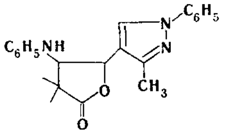
VI

II–IV a R = $CH_2C_6H_5$; b R = CH_3; c R = H

A mixture of reaction products, which could not be separated, is formed in aqueous ethanol solution with ammonium hydroxide, regardless of the molar ratio of the reagents and the temperature. Pyrrolone IVc is obtained when this mixture is refluxed in benzene in the presence of p-toluenesulfonic acid.

The character of the reaction of butenolide I with aniline differs from the character of the reactions examined above. The reaction proceeds only when the reagents are refluxed in dry benzene in the presence of p-toluene sulfonic acid. The set of data from elementary analysis and the IR and PMR spectra attest to the formation of 2-oxo-3,3-dimethyl-5-anilino-5-(1-phenyl-3-methyl-4-pyrazolyl)tetrahydrofuran (V). The carbonyl frequency (1750 cm^{-1}) of the product of the reaction of I with aniline completely excludes lactam structures of the III and IV type but permits the possibility of structure VI. The choice between V and VI was made on the basis of the PMR spectrum (in $CDCl_3$), in which a two-proton signal of the methylene group of V (δ 2.58 ppm) is observed.

EXPERIMENTAL

The IR spectra of hexachlorobutadiene and mineral-oil suspensions of the compounds were recorded with a UR-20 spectrometer.

2,2-Dimethyl-4-keto-4-(1-phenyl-3-methyl-4-pyrazolyl)butanoic Acid Benzylamide (IIa). A solution of 0.54 g (2 mmole) of butenolide I and 0.32 ml (3 mmole) of benzylamine in 5 ml of benzene was refluxed for 2 h, after which it was cooled and 20 ml of hexane was added. The mixture was then allowed to stand at 0° for 12 h, after which it was worked up to give 0.45 g (60%) of amide IIa with mp 102-104° [from benzene–hexane (1 : 1)]. IR spectrum: 3390 (NH), 1660, 1650 (CO), 1600 ($C-C_{arom}$), 1530-1550 cm^{-1} ($C-C_{arom}$ and amide II). Found, %: C 74.0; H 6.8; N 11.3. $C_{23}H_{25}N_3O_2$. Calculated, %: C 73.6; H 6.7; N 11.2.

1-Benzyl-3,3-dimethyl-5-hydroxy-5-(1-phenyl-3-methyl-4-pyrazolyl)-2-pyrrolidone (IIIa). A solution of 0.54 g (2 mmole) of butenolide I and 0.32 ml (3 mmole) of benzylamine in 10 ml of absolute ethanol was refluxed for 6 h, after which it was diluted with 30 ml of water and allowed to stand at 0° for 24 h. The resulting resinous precipitate was recrystallized from benzene–hexane (1 : 3) to give 0.15 g (40%) of pyrrolidone IIIa with mp 153-155°. IR spectrum: 3370 (OH), 1685 (CO), 1600, 1570, and 1510 cm^{-1} ($C-C_{arom}$). Found, %: C 74.1; H 6.6; N 11.4. $C_{27}H_{25}N_3O_2$. Calculated, %: C 73.6; H 6.7; N 11.2.

1-Benzyl-3,3-dimethyl-5-(1-phenyl-3-methyl-4-pyrazolyl)-2,3-dihydro-2-pyrrolone (IVa). A) A 0.54-g (1.4 mmole) sample of amide II was refluxed in 3 ml of acetic anhydride for 2 h, after which the mixture was cooled and poured into 30 ml of water. Workup gave 0.40 g (78%) of pyrrolone IVa with mp 126-128° [from benzene–hexane (1 : 2)]. IR spectrum: 1700 (CO), 1655 (C=C), 1600, 1550, and 1510 cm^{-1} ($C-C_{arom}$). Found, %: C 77.9; H 6.5; N 12.0. $C_{23}H_{23}N_3O$. Claculated, %: C 77.3; H 6.5; N 11.8.

B) A 0.18-g (0.48 mmole) sample of pyrrolidone IIIa was refluxed in 2 ml of acetic anhydride for 2 h. Pyrrolone IVa was isolated as in method A. The yield of product with mp 126-128° was 0.1 g (59%). No melting point depression was observed for a mixture of this product with the product obtained by method A.

1,3,3-Trimethyl-5-hydroxy-5-(1-phenyl-3-methyl-4-pyrazolyl)-2-pyrrolidone (IIIb). A solution of 0.54 g (2 mmole) of butenolide I in 10 ml of ethanol and 0.37 ml of 25% aqueous methylamine was allowed to stand for 2 h, after which it was diluted with 30 ml of water. Workup gave 0.43 g (72%) of pyrrolidone IIIb with mp 153-155° from benzene–hexane). IR spectrum: 3290 (OH), 1670 (CO), 1600, 1570, and 1510 cm^{-1} ($C-C_{arom}$). Found, %: C 67.8; H 7.2; N 14.3. $C_{17}H_{21}N_3O_2$. Calculated, %: C 67.9; H 7.1; N 14.0.

1,3,3-Trimethyl-5-(1-phenyl-3-methyl-4-pyrazolyl)-2,3-dihydro-2-pyrrolone (IVb). This compound, with mp 161-166° [from benzene–hexane (1 : 1)], was obtained in 82% yield by the method used to prepare IVa (A). IR spectrum: 1685 (CO), 1650 (C=C), 1595, 1540, and 1500 cm^{-1} (C–C$_{arom}$). Found, %: C 73.3; H 6.7; N 14.9. $C_{17}H_{19}N_3O$. Calculated, %: C 72.6; H 6.8; N 14.9.

2-Oxo-3,3-dimethyl-5-anilino-5-(1-phenyl-3-methyl-4-pyrazolyl)tetrahydrofuran (V). A solution of 1.08 g (4 mmole) of butenolide I, 0.36 ml (4 mmole) of aniline, and 0.01 g of p-toluenesulfonic acid in 10 ml of dry benzene was refluxed for 6 h, after which the solvent was removed by distillation, and the residue was titurated with 15 ml of hexane. The solid was removed by filtration and recrystallized from benzene–hexane (1 : 1) to give 0.55 g (38%) of lactone V with mp 145-147°. IR spectrum: 3370 (NH), 1750 (lactone CO), 1600, 1560, and 1500 (C–C$_{arom}$), and 1530 cm^{-1} (δ_{NH}). Found, %: C 74.1; H 6.5; N 11.8. $C_{22}H_{23}N_3O_2$. Calculated, %: C 73.1; H 6.4; N 11.6. A total of 0.3 g (28%) of starting I crystallized out from the filtrate (when it was allowed to stand at 0° for 12 h).

3,3-Dimethyl-5-(1-phenyl-3-methyl-4-pyrazolyl)-2,3-dihydro-2-pyrrolone (IVc). A 0.4-ml (3 mmole) sample of 25% ammonium hydroxide was added to a solution of 0.54 g (2 mmole) of butenolide I in 6 ml of ethanol at 30-40°, and the mixture was allowed to stand at 20-25° for 24 h. It was then diluted with 30 ml of water and allowed to stand for another 72 h. The precipitate was recrystallized from benzene to give 0.4 g of a substance with mp 150-170°. This product was refluxed in 30 ml of dry benzene in the presence of 0.02 g of p-toluenesulfonic acid. When the mixture was cooled, 0.35 g (64%) of pyrrolone IVc with mp 181-183° (from benzene) crystallized out. IR spectrum: 3150-3220 (NH), 1710 (CO), 1660 (C=C), and 1600, 1550, and 1510 cm^{-1} (C–C$_{arom}$). Found, %: C 72.3; H 6.5; N 15.6. $C_{16}H_{17}N_3O$. Calculated, %: C 71.9; H 6.4; N 15.7.

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