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N-3-OXOALKYLAMIDES AND -THIOAMIDES IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS
5*. SYNTHESIS OF 1-(4-HYDROXY-2-OXO-3-PIPERIDYL)-PYRIDINIUM CHLORIDES AND 2-PYRIDONES FROM PYRIDINIUM DERIVATIVES OF N-3-OXOALKYLCHLOROACETAMIDES

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2-Pyridones and 1-(4-hydroxy-2-oxo-3-piperidyl)pyridinium chlorides have been obtained by the intramolecular cyclization of N-3-oxoalkylchloroacetamides under the action of tertiary amines.

N-3-Oxoalkylphenylacetamides are cyclized by the action of base into the corresponding 3-phenyl-5,6-dihydropyridin-2(1H)-ones [2]. It is evident that a necessary condition for this reaction is adequate CH acidity at the position relative to the carbamoyl group of the N-3-oxoalkylacetamide. This may be provided by replacing the carbamoyl function by thiocarbamoyl [3] or by the presence of an electron-attracting substituent (such as pyridinium cation) at this position. Pyridinium derivatives of N-3-oxoalkylacetamides may be obtained from the readily available N-3-oxoalkylchloroacetamides [4-8].

We obtained the previously unknown 1-(3-oxoalkyl-carbamoylmethyl)pyridinium chlorides (IIa-d) in 88-96% yield by the reaction of N-3-oxoalkylchloroacetamides (Ia-d) with pyridine at room temperature. Compounds (IIa-c) were converted by the action of triethylamine in DMF at room temperature into 1-(4-hydroxy-2-oxo-3-piperidyl)pyridinium chlorides (IIIa-c) in 88-90% yield. Compounds (IIIa-c) are probably formed by intramolecular cyclization of the corresponding pyridinium ylids generated from pyridinium salts (IIa-c) by the action of the triethylamine in the reaction mixture.

Heating compounds (Ic,d) in a mixture of pyridine and DMF and also compounds (IIc,d) in methanol in the presence of triethylamine leads to the formation of 4,6-diphenylpyridin-2(1H)-one (VIIc) and 1-phenyl-4,5,6,7-tetrahydro-3-isoquinolone (VIId) respectively. However, under analogous conditions N-(1-methyl-3-oxobutyl)chloroacetamide (Ib) and 1-(1-methyl-3-oxobutylcarbamoylmethyl)pyridinium chloride (IIb) form 1-(4-hydroxy-4,6-dimethyl-2-piperidon-3-yl)pyridinium chloride (IIIb) and not the expected 4,6-dimethyl-2-piperidone.

The conversion of compound (II) into pyridone (VII) is probably favored by the increase in the effective volume of the substituent R^1 causing a reduction in the stability of compound (III). In its turn an increase in the acidity of position 6 of the heterocycle assists the isomerization of the intermediately formed dihydropyridin-2(1H)-one (V) into 1-(2-oxo-1,2,3,4-tetrahydro-3-pyridyl)pyridinium chloride (VI). Fission of pyridine hydrochloride from pyridinium salts analogous to compound (VI) is well known [9,10].

We have therefore shown that the degree of conversion of pyridinium salts (II) under the action of base depends on the reaction conditions and the structure of the initial compound. A new method has been found for synthesizing 2-pyridones from available precursors, (4-hydroxy-2-oxo-3-piperidinyl)pyridinium chlorides have been obtained for the first time.

*For part 4 see [1].

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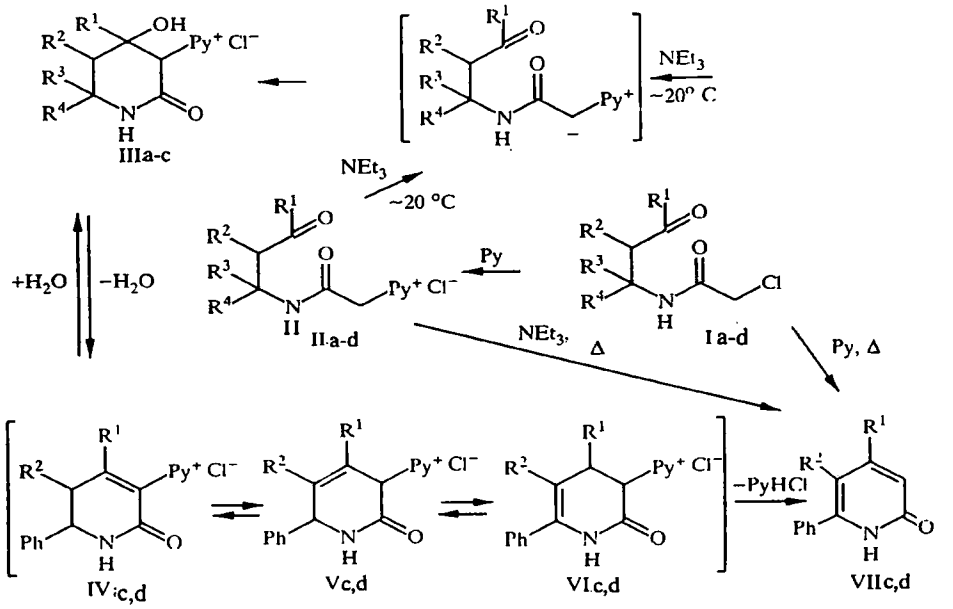

I–VII a $R^1 = R^3 = R^4 = Me$, $R^2 = H$; b $R^1 = R^4 = Me$, $R^2 = R^3 = H$;
c $R^1 = R^4 = Ph$, $R^2 = R^3 = H$; d R^1, $R^2 = (-CH_2-)_4$, $R^3 = H$;
$R^4 = Ph$

EXPERIMENTAL

The PMR spectra were measured on a Bruker AC 200 spectrometer, internal standard was TMS.

N-3-oxoalkylchloroacetamides (Ia-d) were synthesized by the procedure of [2]. Compounds (Ia,b) were obtained from the corresponding 1,3-aminoketone hydrochlorides and chloroacetyl chloride in 85% yield for (Ia) (bp 111-115°C/5 mm Hg), and 48% for (Ib) (mp 42-43°C, from hexane). Compounds (Ic,d) were obtained from the corresponding 1,3-chloroketones and chloroacetonitrile in 81% yield for (Ic) (mp 103-104°C, from ethanol) and 30% for (Id) (mp 157-158°C, from ethanol).

The PMR spectral data for compounds (Ia-d) confirmed the structures of the compounds obtained.

1-(3-Oxoalkylcarbamoylmethyl)pyridinium Chlorides (IIa-d). N-3-oxoalkylchloroacetamide (I) (2 mmole) in pyridine (3 ml) was left for 24 h at room temperature. The reaction mixture was then diluted with ether (10 ml), the precipitated solid was filtered off, and washed with dry ether (5 ml). The yield of (IIa) was 96%, (IIb) 96%, (IIc) 92%, and (IId) 88%.

The PMR Spectrum (CD_3OD) of Compound (IIa): 9.64 (1H, br s, NH); 8.12-8.92 (5H, m, Py); 5.40 (2H, s, CH_2-Py); 3.01 (2H, s, OC-CH_2); 2.10 (3H, s, CH_3-CO); 1.40 ppm (6H, s, CH_3-s-CH_3); compound (IIb): 9.44 (1H, br s, NH); 9.03-9.21 (5H, m, Py); 5.59 (2H, s, CH_2-Py); 4.12-4.31 (1H, m, CH_3-CHX-NH); 3.46 (1H, A of ABX, $^2J_{AB}$ = 16.8, $^3J_{BX}$ = 6.8 Hz, CH_AH_B-CO); 3.25 (1H, B of ABX, $^2J_{AB}$ = 16.8, $^3J_{AX}$ = 6.8 Hz, CH_AH_B-CO); 2.10 (3H, s, CH_3-CO); 1.16 ppm (3H, d, ^3J = 6.6 Hz, CH_3-CHX-NH); compound (IIc): 9.97 (1H, br s, NH); 7.96-8.90 (5H, m, Py); 7.24-7.61 (10H, m, 2 × Ph); 5.56 (1H, X of ABX, Ph-CHX-NH); 5.49 (2H, s, CH_2-Py); 3.74 (1H, A of ABX, $^2J_{AB}$ = 17.4, $^3J_{BX}$ = 8.1 Hz, CH_AH_B-CO); 3.56 ppm (1H, B of ABX, $^2J_{AB}$ = 17.4, $^3J_{AX}$ = 5.8 Hz, CH_AH_B-CO); compound (IId): 9.81 (1H, br s, NH); 7.96-8.90 (5H, m, Py); 7.41-7.45 (5H, m, Ph); 5.49 (2H, s, CH_2-Py); 5.25 (1H, d d, $^3J_{NH}$ = 9.5, ^3J = 4.0 Hz, Ph-CH); 3.30 (1H, m, Ph-CH-CH-CO); 1.76-2.53 (8H, m, 4 × CH_2); 2.3 ppm (2H, m, 4-CH_2). Data of elemental analysis. (IIa): Found, %: C 57.72; H 7.10; N 10.34. $C_{13}H_{19}ClN_2O_2$. Calculated, %: C 57.67; H 7.07; N 10.35. (IIb): Found, %: C 56.32; H 6.77. $C_{12}H_{17}ClN_2O_2$. Calculated, %: C 56.14; H 6.67. (IIc): Found, %: C 69.52; H 5.60. $C_{22}H_{21}ClN_2O_2$. Calculated, %: C 69.38; H 5.56. (IId): Found, %: C 67.04; H 6.46. $C_{20}H_{23}ClN_2O_2$. Calculated, %: C 66.94; H 6.46.

1-(4-Hydroxypiperid-2-on-3-yl)pyridinium Chlorides (IIIa,b). Triethylamine (0.05 ml) was added to a solution of 1-(3-oxoalkylcarbamoylmethyl)pyridinium chloride (II) (4 mmole) in the minimum amount of DMF (3-4 ml) at 0-5°C. The reaction mixture was left at room temperature for 48 h. The precipitate was filtered off and washed with dry ether (5 ml). Compound (IIIa) was obtained in 90% yield and (IIIb) in 88%.

The PMR Spectrum (CD_3OD) of Compound (IIIa): 8.13-9.00 (5H, m, Py); 5.89 (1H, s, 3-CH); 1.29 [3H, s, 6-$(CH_3)_a$]; 1.54 (3H, s, 4-CH_3); 2.18 (2H, s, 5-CH_2); 1.13 ppm [3H, s, 6-$(CH_3)_e$]: compound (IIIb): 9.18-10.00 (5H, m, Py); 5.90 (1H, s, CH-Py); 3.92-4.03 (1H, m, CH_3-CH_X-NH); 2.21 (1H, A of ABX, $^2J_{AB}$ = 14.3, $^3J_{AX}$ = 4.5 Hz, CH_AH_B-CH_X-CH_3); 1.99 (1H, A of ABX, $^2J_{AB}$ = 14.3, $^3J_{AX}$ = 11.2 Hz, CH_ACH_B-CH_X-CH_3); 1.33 (3H, d, J = 7.3 Hz, CH_3-CH_X-NH); 1.20 ppm (3H, s, CH_3-C-OH). Data of elemental analysis of (IIa): Found, %: C 57.68; H 7.12. $C_{13}H_{19}ClN_2O_2$. Calculated, %: C 57.67; H 7.07. (IIIb): Found, %: 56.22; H 6.74. $C_{12}H_{17}ClN_2O_2$. Calculated, %: C 56.14; H 6.67.

4,6-Diphenylpyrid-2(1H)-one (VIIc) and 1-Phenyl-5,6,7,8-tetrahydro-3-isoquinolone (VIId). A. A mixture of N-3-oxoalkylchloroacetamide (I) (4 mmole), pyridine (0.5 ml), and DMF (0.5 ml) was boiled for 3 h, and the reaction mixture was then poured into water (30 ml). The precipitated solid was filtered off, washed with water, and dried in vacuum. Compound (VIIc) was obtained in 42% yield, compound (VIId) in 24%.

B. Triethylamine (0.15 ml) was added to a solution of 1-(3-oxoalkylcarbamoylmethyl)pyridinium chloride (II) (4 mmole) in methanol (3 ml) and the mixture boiled for 1 h. The methanol was evaporated under reduced pressure. The residue was washed with water, filtered off, and dried in vacuum. Compounds (VIIc) and (VIId) were obtained in 79 and 58% yield respectively. PMR spectrum (DMSO-D_6) compound (VIIc): 7.28-7.80 (10H, m, 2 × Ph); 6.84 (1H, d, $^4J_{35}$ = 1.6 Hz, 3-CH); 6.50 ppm (1H, d, $^4J_{35}$ = 1.6 Hz, 5-CH); compound (VIId): 7.41-7.45 (5H, m, Ph); 6.13 (1H, s, 3-CH); 2.65 (2H, m, 7-CH_2); 1.57-1.65 (4H, m, 5-CH_2 and 4-CH_2); 2.31 ppm (2H, m, 6-CH_2). Data of elemental analysis of (VIIc): Found, %: C 80.02; H 6.74. $C_{15}H_{15}NO$. Calculated, %: C 79.97; H 6.71. The melting point of compound (VIIc) (211-212°C) agreed with that reported in [11].

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