SUBSTITUTION OF 3H-FURAN-2-ONES IN AMINATION AND HYDROAMINATION REACTIONS

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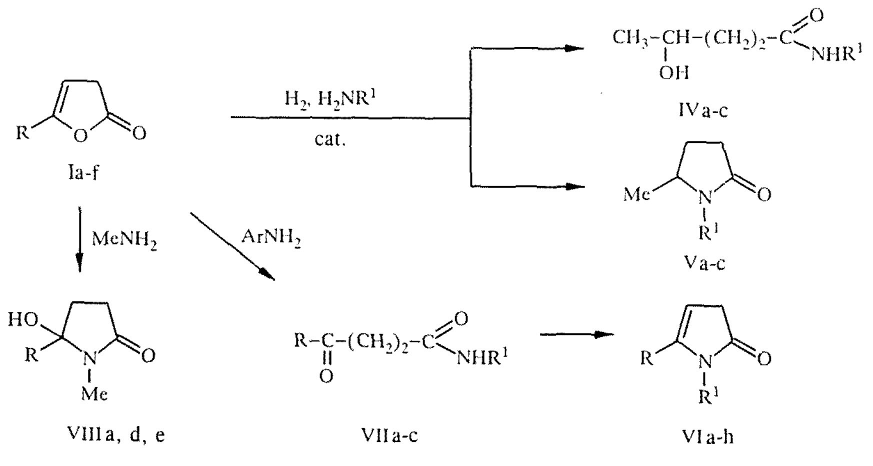
The amination and hydroamination of 5-alkyl-3H-furan-2-ones and their 3-benzylidene- and 3-formyl-derivatives were studied. The characteristics of the reactions, the requirements for the nature of the nucleophilic reagents, and the reaction conditions leading to the destruction of the furan ring and recyclization to pyrrolidinone and pyrrolinone structures are indicated.

The reaction of 3H-furan-2-ones with amines is worthy of attention in planning a synthesis of azaheterocyclic compounds such as pyrrolines and pyrrolidones carrying pharmacophoric fragments. In a continuation of investigations of 5-alkyl-3H-furan-2-ones [1, 2] we studied the reaction of some of them (Ia-f) and also their 3-arylidine (IIa-c) or 3-formyl derivatives (IIIa, b) under amination and hydroamination conditions.

The reductive amination of 5-methyl-3H-furan-2-one Ia at 20-100°C under a hydrogen pressure of 80-100 atm over Rainey nickel with amination reagents (ammonia, methylamine, aminoethanol) leads to noncyclic amides of 4-hydroxypentanoic acid (IVa-c). A higher temperature (120-150°C, initial hydrogen pressure of 120 atm) gives the formation of azaheterocycles; 1-R′-5-methyl-2-pyrrolidones (Va-c). The substitution of a nickel boride catalyst for Rainey nickel allows the recyclization process to take place at 150°C and 100 atm hydrogen pressure.

Scheme



I, VIIIa R = CH_3, b R = C_4H_9, c R = i-C_4H_9, d R = C_5H_{11}, e R = C_6H_{13}, f R = C_7H_{15}; IV, Va R^1 = H, b R^1 = CH_3, c R^1 = $(CH_2)_2OH$; VIa–c R^1 = CH_2Ph, a R = CH_3, b R = C_4H_9, c R = i-C_4H_9; VId–h R^1 = Ph, d R = CH_3, e R = i-C_4H_9, f R = C_5H_{11}, g R = C_6H_{13}, h R = C_7H_{15}; VIIa R = CH_3, R^1 = CH_2Ph; b R = C_7H_{15}, R^1 = C_6H_4Br-p; c R = C_7H_{15}, R^1 = C_6H_4Br-p

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TABLE 1. Characteristics of Compounds IV-IX

Compound	bp, °C/mm Hg or mp, °C	n_D^{20}	IR spectrum, ν, cm^{-1}	Yield, %
IVa	60...61/8	1,4590	3500, 1630, 1550, 3390	72
IVb	93...95/14	1,4592	3500, 1670, 1580, 3390	69
IVc	110...112/8	1,4830	3500, 1590, 3390	93
Va	138...139/15	1,4610	2900, 1690	75
Vb	102...104/17	1,4405	3000, 1700	83
Vc	177...178/13	1,4835	3000, 1670	80
VIa	173...175/5	1,5381	1700, 1610	62
VIb	159...160/5	1,5280	1710, 1600	63
VId	158...160/5	1,5325	1700, 1610	70
VIe	172...173/5	1,5328	1710, 1600	72
VIc	165...167/5	1,5330	1705, 1605	75
VIf	160...162/5	1,5340	1710, 1610	65
VIg	168...170/5	1,5346	1705, 1600	71
VIh	166...168/5	1,5380	1700, 1600	65
VIIa	67...69	—	3330, 1695, 1550	80
VIIb	55...56	—	3335, 1695, 1557	70
VIIc	52...53	—	3330, 1700, 1555	74
VIIIa	98...100/5	1,4650		67
VIIIb	120...121/5	1,4692		72
VIIIc	132...134/5	1,4710		70
IXa	82...84	—	1715, 1620	73
IXb	89...91	—	1710, 1617	66
IXc	104...106	—	1710, 1620	81

TABLE 2. ^{1}H NMR Spectra of Compounds VIII and X

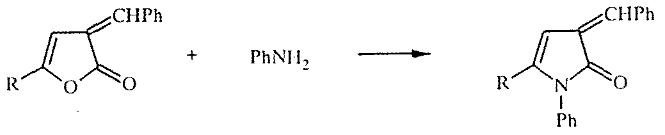
Compound	^{1}H NMR spectrum, ppm; coupling constants, J, Hz			
	3-H	4-H or =CHN*	N-CH$_3$ or NH*^{2}, s	OH, s
VIIIa	2,15 (2H), q, $J = 17{,}38$	1,91 (2H), q	1,46 (3H)	5,38 (1H)
VIIId	2,15 (2H), q, $J = 17{,}38$	1,95 (2H), q	1,46 (3H)	5,38 (1H)
VIIIe	2,17 (2H), q, $J = 17{,}40$	1,91 (2H), q	1,46 (3H)	5,38 (1H)
Xa	6,26 (1H), s	7,20 (1H)*, s, $J = 12{,}5$	10,84 (1H)*^{2}, s	—
Xb	6,32 (1H), s	7,22 (1H)*, s, $J = 12{,}5$	10,87 (1H)*^{2}, s	—

The amination of 5-R-3H-furan-2-ones Ia-f with aniline and benzylamine by boiling in xylene gives the 1-R′-5-R-3H-pyrrolin-2-ones (VIa-h). The reaction proceeds with the cleavage of the lactone ring. At a lower temperature (boiling in benzene) and shorter reaction time the process gives the amides VIIa-c from Ia, d, f and benzylamine or n-bromoaniline.

With a stronger nucleophile (CH_3NH_2), the 3H-furanones Ia, d, e react in an aqueous alcoholic medium at 40-45°C with the formation of 1-Me-5-alkyl-5-hydroxy-2-pyrrolidones (VIIIa, d, e) which are the cyclic forms of the intermediate 3-ketocarboxamides (see Scheme).

The structures of the compounds IV-VIII were confirmed by IR and ^{1}H NMR spectroscopy. The basic proofs of the cyclic forms of compounds Va-c are the absence in the IR of the amide-II bands ($\nu_{C-N} + \delta_{N-H}$) at 1520-1570 cm^{-1} and the presence of intense absorption bands of the lactam carbonyl at 1710-1720 cm^{-1} and the OH group at 3350-3500 cm^{-1}. The ^{1}H NMR spectra of compounds VIII showed a quadruplet signal of the C-3 and C-4 methylene protons, and also singlet signals of the CH_3 on the nitrogen atom at 1.46 and the proton of the HO group at 5.38 ppm. The IR spectra of compounds VIa-h contained absorption bands for the lactam carbonyl at 1700-1710 cm^{-1} and absorption bands for the C=C in the 1600-1610 cm^{-1} region. The spectra of the hydroxyamides IVa-c contained absorption bands for the NH group at 3300-3390, the OH group at 3500, the amide I and amide II bands at 1690-1700 and 1550-1560 cm^{-1}. The amides VIIa-c showed absorption bands for the NH at 3300-3335 and the amide I and amide II at 1670-1695 and 1550-1557 cm^{-1}.

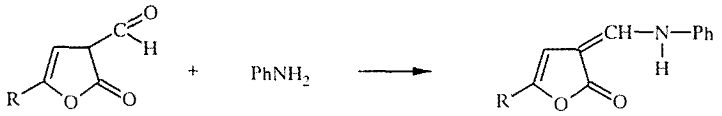
The character of the substituent in position 3 of the lactone ring determines the direction of the reaction of the earlier synthesized compounds IIa-c [1] with aniline. This showed the possibility of the synthesis from 3-benzylidene-3H-furanones of the recyclization products 3-benzylidine-5R-pyrrolin-2-ones (IXa-c).



II a-c IX a-c

II, IX a R = CH_3, b R = i-C_4H_9, c R = Ph

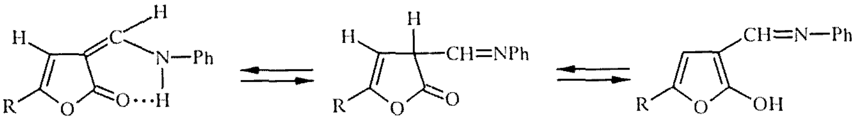
For the case of the known 3-formyl-3H-furan-2-ones IIIa, b [2], the reaction with aniline took place only on the formyl group with the conservation of the cyclic structure to give the corresponding Schiff base (Xa, b).



IIIa,b Xa,b

III, X a R = C_5H_{11}, b R = C_6H_{13}

On the basis of IR and ^{1}H NMR spectral data it is possible to conclude the existence of product X in $CDCl_3$ solution as the tautomeric form A because of stabilization by intramolecular hydrogen bonds.



A B C

Thus, the spin–spin coupling constants between the protons of the =CHN fragment and the NHPh (J = 12.5 Hz) indicates the localization of the protons on the nitrogen atom. The IR spectra of compounds Xa, b shows wide bands at 3220-3350 cm^{-1}, which must be related to the vibration of the NH group involving the intramolecular hydrogen bond.

EXPERIMENTAL

The IR spectra were recorded with a IKS-29 instrument in mineral oil and hexachlorobutadiene. The ^{1}H NMR spectra were obtained with a Varian FT-80A in $CDCl_3$, using HMDS as internal standard. The integrity of the synthesized compounds was controlled by TLC on Silufol UV-254 plates in a benzene–acetone–chloroform 4:1:1 system. The starting materials Ia-f and IIa-c were described in [1], and IIIa, b in [2]. The characteristics of the synthesized compounds are presented in Tables 1 and 2. The results of elemental analyses for C, H, and N corresponded with the calculated values.

Amides of γ-Hydroxypentanoic Acid (IVa-c). An autoclave was charged with 0.1 mole of 3H-furanone Ia, 100 ml of ethanol saturated with ammonia, methylamine or containing 0.1 mole of aminoethanol. The hydroamination was carried out over Rainey nickel at 100°C and initial hydrogen pressure of 100 atm. Then the solvent was removed and the residue was distilled under vacuum to give the products IVa-c.

1-R^1-5-Methyl-2-pyrrolidones (Va-c). Compounds Va-c were synthesized analogously from 0.1 mole of Ia at 120-150°C and initial hydrogen pressure of 120 atm. They were also obtained in yields of 32-34% by the described method using nickel boride catalyst from 0.1 mole of Ia at 150°C under initial hydrogen pressure of 100 atm.

1-R^1-5R-3H-2-Pyrrolinones (VIa-h). A mixture of 0.02 mole of 3H-2-furanone Ia and 0.1 mole of aniline or benzylamine in absolute xylene was boiled for 3 h. The solvent was removed and the residue was fractionated under vacuum to give products VIa-h.

N-R^1-Amides of 3-R-3-ketocarboxylic Acids (VIIa-c). A mixture of 0.025 mole of 3H-furanone I and 0.038 mole of benzylamine or n-bromoaniline was boiled in benzene for 1 h, the reaction mixture was cooled to 0°C and the precipitated VIIIa-c was filtered off. For purification, 0.04 mole of amide VII was boiled in 50 ml of acetic anhydride for 1 h, then the solvent was removed under reduced pressure, and the residue was fractionated under vacuum to give VIIa-c.

5-Hydroxy-1-methyl-5-R-2-pyrrolidones (VIIIa-c). To a solution of 0.012 mole of 3H-furanone Ia in 6-10 ml of ethanol at 40°C was added 10 ml of 25% aqueous alcoholic methylamine solution. The mixture was kept for 48 h at room temperature, the reaction mixture was then extracted with toluene, the solvent was evaporated, and the residue was distilled under vacuum to give VIII.

1-Phenyl-5-R-3-benzylidene-3H-2-pyrrolinones (IXa-c). A mixture of 0.1 mole of benzylidine derivative IIa-c and 0.1 mole of aniline was boiled for 2 h, 15 ml of acetic anhydride was added, the boiling was continued for another 1h and cooled to give IXa-c.

Schiff Bases (Xa, b). The reaction mixture from 0.026 mole of 3-formyl-3H-furanone (IIIa, b) and 0.035 mole of aniline in 20-25 ml of benzene was kept at 80°C for 2 h. The resulting crystals of Xa, b were filtered off and washed with ether.

REFERENCES

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2. V. A. Sedavkina, N. A. Morozova, and A. Yu. Egorova, Khim. Geterotsikl. Soedin., No. 4, 456 (1993).