Raman spectra were obtained on a Romanor-1000 spectrometer with a laser excitation source (λ_{excit} = 514.5 nm, S = 500 μ). Solid phase samples Ia, e, f (20 mg) were mixed with KBr (200 mg) and pressed. The liquid sample IIe was recorded neat.

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SYNTHESIS AND STRUCTURE OF 3-OXOPYRANO[3,4-c]PYRIDINES

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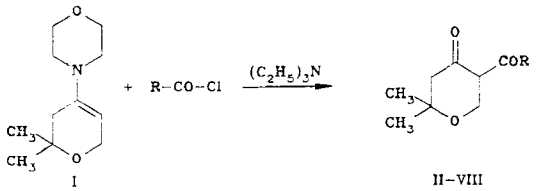
UDC 547.816+547.83

Acylation of the enamine of 2,2-dimethyltetrahydropyran-4-one with acid chlorides produced α-acylpyran-4-ones which give 3-oxopyrano[3,4-c]pyridines when treated with cyanoacetamide.

In our search for new biologically active condensed pyridines [1, 2] we have developed a method for preparing 3-oxopyrano[3,4-c]pyridines from 2,2-dimethyl-4-(N-morpholino)-2,3-dihydro-6H-pyran (I).

Reaction of enamine I with acid chlorides under Stork conditions gave the corresponding α-acylpyran-4-ones II-VIII



I II–VIII

II R=CH_3; III R=C_3H_7; IV R=i-C_3H_7; V R=C_6H_5; VI R=o-ClC_6H_4; VII R=p-ClC_6H_4; VIII R=CCl_3

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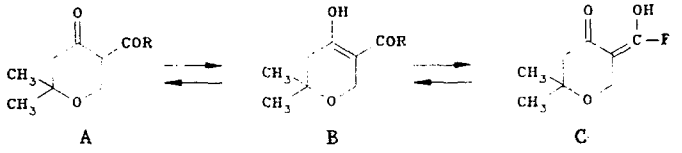
TABLE 1. α-Acylpyran-4-ones II-VIII

Compound	Empirical formula	bp, °C (mm Hg)	IR spectrum, cm^{-1}	Yield, %
II	$C_9H_{14}O_3$	128...130 (20)	1730, 1690 (C=O), 1600 ($C=C_{arom}$)	55
III	$C_{11}H_{18}O_3$	162...163 (1)	1740, 1680 (C=O), 1610 ($C=C_{arom}$)	26
IV	$C_{11}H_{18}O_3$	120...122 (6)	3200...3500 (OH), 1740, 1690 (C=O), 1620 ($C=C_{arom}$)	39
V	$C_{14}H_{16}O_3$	170...172 (2)	1690, 1670 (C=O), 1590 ($C=C_{arom}$)	56
VI	$C_{14}H_{15}ClO_3$	160...162 (1)	1740, 1690 (C=O), 1590 ($C=C_{arom}$)	36
VII	$C_{14}H_{15}ClO_3$	140...143 (1)	1750, 1670 (C=O), 1600 ($C=C_{arom}$)	35
VIII	$C_9H_{11}Cl_3O_3$	103...104*	1760, 1720 (C=O)	35

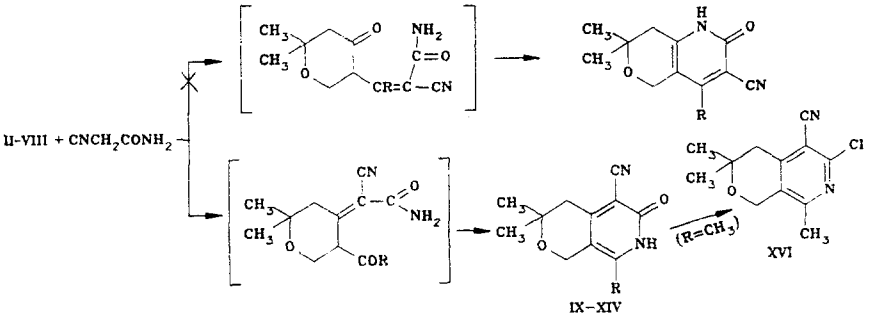
*mp, °C.

It is known that keto-enol tautomerism is observed in α-acylcyclohexanones [3]. In six membered rings the tautomer with an endocyclic double bond predominates [4]. The IR and PMR spectral data on the present series of α-acylpyran-4-ones point to an analogous tautomerism.



The weighting of the tautomeric forms in compounds II-VIII depends upon the nature of the acyl residue. NMR Spectra recorded for II (R = CH_3) in CCl_4 solvent have shown that it exists in the enol form (B) as evidenced by the triplet signals for the methylene groups in the pyranone ring (near 4.3 and 2.1 ppm). In the case of an electron acceptor substituent (VIII, R = CCl_3) the forms A and B are dominant. For pyranone V (R = Ph) no particular isomer is dominant but the B forms predominate for VI and VII with an electron accepting chlorine in the ortho- or para- position of the benzene ring. The IR spectra of II-VIII show absorptions characteristic of the enol C=C bonds at 1590-1630 cm^{-1}. In II, III, and V-VIII, as in α-aroylcyclohexanones [5], the absorption characteristic of the OH group is not seen due to powerful hydrogen bonding. Absorption bands due to the carbonyl group are seen in the regions 1650-1720 and 1730-1760 cm^{-1}.

β-Dicarbonyl compounds are starting materials for pyridine syntheses. It is known that 2,6-dimethyl-3-formyltetrahydropyran-4-one cyclizes with cyanoacetamide to give pyrano-[4,3-b]pyridines [6] and that 2,6-dimethyl-3-carbethoxytetrahydropyran-4-one gives pyrano-[3,4-c]pyridines [7]. There have been no reports of the cyclization of α-acylpyran-4-ones. We have brought this about by treating II-VIII with cyanoacetamide in the presence of diethylamine.



IX R=CH_3, X R=C_3H_7, XI R=i-C_3H_7, XII R=C_6H_5, XIII R=o-ClC_6H_4, XIV R=p-ClC_6H_4

The product yield depends on the nature of the acyl substituent and for R = CCl_3 the condensed pyridine was not formed. The IR spectra of the products show carbonyl group absorptions near 1650 cm^{-1}, nitrile groups near 2240 cm^{-1}, and weak NH vibrations in the region 3100-3250 cm^{-1}. The PMR spectra of the condensation products showed signals for methylene groups in the pyran ring as triplets in the regions 4.3-4.9 and 2.6-2.8 ppm.

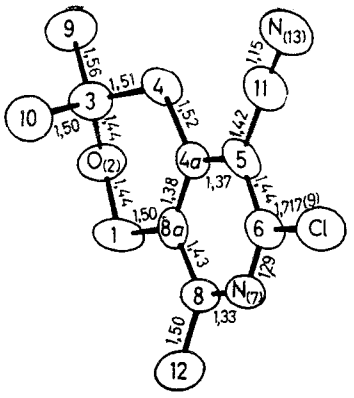
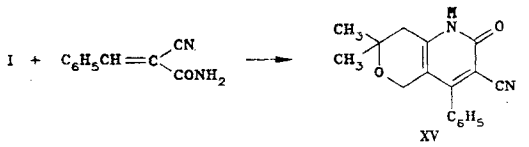


Fig. 1. Structure and bond lengths for the pyrano[3,4-c]pyridine XVI, σ = 0.01 Å.

However, it is not possible to determine the position of the fusion of the pyran and pyridine rings on the basis of the spectral data. Attack of the cyanoacetamide active methylene group can occur at the carbonyl fragment either in the pyran ring or in the acyl group. For R = H attack is exclusively at the aldehyde group [6]. In the case of β-diketones both variants are possible although it is known that the ketonic carbonyl groups in six membered cyclic ketones are more reactive than in aliphatics [8]. Based on the latter we have proposed that reaction of II-VIII with cyanoacetamide leads to the 3-oxopyrano[3,4-c]pyridines IX-XIV and this was confirmed both by an independent synthesis and by X-ray structural analysis.

Reaction of the morpholine enamine of cyclohexanone with benzylidenecyanothioacetamide is known to form tetrahydroquinolines [9]. We have carried out a similar condensation of enamine I with benzylidenecyanoacetamide to give 2-oxopyrano[4,3-b]pyridine XV.



The melting points of XII and XV differ by 25°C. Their IR and mass spectra are identical but the PMR signals for XV were shifted to slightly higher field. The UV spectra of XII and XV showed identical absorptions at 242 and 348 nm but only XV showed a band at 277 nm (which is apparently a result of the interaction of the ortho-related nitrile and phenyl groups).

Monocrystals of IX-XIV could not be prepared for x-ray structural analysis hence the chloro derivative XVI was prepared by treating IX with phosphorous oxychloride. As a result it was unambiguously shown that the reaction products of II-VIII with cyanoacetamide are the pyrano[3,4-c]pyridines (Fig. 1). The geometrical parameters for molecule XVI in the range 3σ agree well with standard values and do not demand special comment. The pyran ring shows a strong half chair conformational distortion, the deviations of the atoms $O_{(2)}$ and $C_{(3)}$ being −0.197(6) and 0.524(8) Å from the mean plane of the remaining ring atoms. The pyridine ring is planar (the largest deviation from the mean plain of the ring being 0.016(8) Å for atom $C_{(4a)}$). The molecular crystal is stabilized by van der Waal forces as evidenced by the absence of intermolecular contacts for the least sums of the van der Waal radii of the corresponding atoms.

EXPERIMENTAL

IR Spectra were recorded on a UR-20 instrument in a vaseline mull and UV spectra on a Specord UV-vis instrument using methanol solvent. PMR Spectra were measured on a Varian T-60 and mass spectra on an MK-1303 with an ionization intensity of 70 eV. TLC was carried out on Silufol UV-254 plates using the systems pyridine:ethanol (1:2, IX, XII) or butanol: acetic acid:water (4:2:5, X, XI, XIII, XIV) with visualization by iodine vapor.

Elemental analytical data agreed with that calculated.

TABLE 2. 3-Oxopyrano[3,4-c]pyridines IX-XIV

Compound	Empirical formula	mp, °C	R_f	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm	Yield, %
IX	$C_{12}H_{14}N_2O_2$	308...309	0,56	3420 (NH), 2220 (CN), 1670 (C=O), 1620 (C=C$_{arom}$)	4,6 (2H, t, CH_2O); 2,7 (2H, t, CH_2); 2,2 (3H, s, CH_3); 1,3 (6H, s, 2CH_3)	58
X	$C_{11}H_{18}N_2O_2$	253...254	0,54	3150 (NH), 2230 (CN), 1650 (C=O), 1600 (C=C$_{arom}$)	4,5 (2H, t, CH_2O); 2,6 (2H, t, CH_2); 2,4 (2H, t, $CH_2C_2H_5$); 1,6 (2H, q, CH_2CH_3); 1,3 (6H, s, 2CH_3); 0,9 (3H, t, CH_2CH_3)	27
XI	$C_{14}H_{18}N_2O_2$	288...289	0,54	3390 (NH), 2230 (CN), 1650 (C=O), 1600 (C=C$_{arom}$)	4,6 (2H, t, CH_2O); 2,9 (1H, q, CH); 2,7 (2H, t, CH_2); 1,3 (6H, s, 2CH_3); 1,2 (6H, d, $CH(CH_3)_2$)	43
XII	$C_{17}H_{16}N_2O_2$	274...275	0,64	3370 (NH), 2230 (CN), 1640 (C=O), 1600 (C=C$_{arom}$)	7,6 (5H, s, C_6H_5); 4,4 (2H, t, CH_2O); 2,8 (2H, t CH_2); 1,3 (6H, s, 2CH_3)	60
XIII	$C_{17}H_{15}N_2ClO_2$	272...273	0,59	3400 (NH), 2240 (CN), 1640 (C=O), 1610 (C=C$_{arom}$)	7,6 (4H, s, C_6H_4); 4,1 (2H, t, CH_2O); 2,9 (2H, t, CH_2); 1,2 (6H, s, 2CH_3)	28
XIV	$C_{17}H_{15}N_2ClO_2$	284...285	0,50	3410 (NH), 2230 (CN), 1640 (C=O), 1580 (C=C$_{arom}$)	7,7 (4H, s, C_6H_4); 4,3 (2H, t CH_2O); 2,7 (2H, t CH_2); 1,1 (6H, s, 2CH_3)	25

TABLE 3. Atomic Coordinates × 10^4 and Their Equivalent Temperature Parameters

Atom	x/a	y/b	z/c	B^{equ}_{iso}	Atom	x/a	y/b	z/c	B^{equ}_{iso}
Cl	7495(2)	2671(4)	4576(2)	6,0	$N_{(7)}$	5537(5)	2542(10)	4273(4)	3,8
$C_{(1)}$	3595(7)	−720(14)	2892(7)	4,9	$C_{(8)}$	4651(7)	1818(13)	3906(6)	3,8
$C_{(2)}$	3644(4)	−2690(8)	2430(4)	4,4	$C_{(8a)}$	4607(6)	−17(12)	3334(5)	3,3
$C_{(3)}$	4506(7)	−2982(13)	1850(6)	4,0	$C_{(9)}$	4370(8)	−5166(14)	1405(7)	5,5
$C_{(4)}$	5458(6)	−2928(12)	2522(6)	3,8	$C_{(10)}$	4531(8)	−1435(14)	1043(7)	5,4
$C_{(4a)}$	5498(6)	−999(13)	3152(6)	3,1	$C_{(11)}$	7325(7)	−1253(14)	3433(6)	4,6
$C_{(5)}$	6396(6)	−241(13)	6562(6)	3,8	$N_{(12)}$	8075(6)	−2092(13)	3338(6)	6,4
$C_{(6)}$	6371(6)	1626(13)	4113(6)	4,0	$C_{(13)}$	3715(7)	2983(14)	4112(6)	5,3

TABLE 4. Valence Angles ω

Angle	ω(σ)°	Angle	ω(σ)°	Angle	ω(σ)°
$C_{(1)}O_{(2)}C_{(3)}$	114,8(6)	$C_{(4)}C_{(3)}C_{(10)}$	112,0(7)	$C_{(8a)}C_{(4a)}C_{(5)}$	119,1(8)
$C_{(2)}C_{(3)}C_{(4)}$	106.6(7)	$C_{(9)}C_{(3)}C_{(10)}$	109,7(7)	$C_{(5)}C_{(11)}N_{(12)}$	179,1(9)
$C_{(3)}C_{(4)}C_{(4a)}$	111,1(7)	$C_{(4)}C_{(4a)}C_{(5)}$	121,7(7)	$C_{(4a)}C_{(5)}C_{(11)}$	121,0(8)
$C_{(4)}C_{(4a)}C_{(8a)}$	119,2(7)	$C_{(1)}C_{(8a)}C_{(8)}$	118,6(7)	$C_{(6)}C_{(5)}C_{(11)}$	120,8(8)
$C_{(4a)}C_{(8a)}C_{(1)}$	122,3(7)	$C_{(4a)}C_{(5)}C_{(6)}$	118,2(8)	$C_{(5)}C_{(6)}Cl$	118,8(6)
$C_{(8a)}C_{(1)}O_{(2)}$	112,7(7)	$C_{(5)}C_{(6)}N_{(7)}$	122,3(8)	$N_{(7)}C_{(6)}Cl$	118,9(6)
$C_{(2)}C_{(3)}C_{(9)}$	105,1(7)	$C_{(6)}N_{(7)}C_{(8)}$	120,9(7)	$N_{(7)}C_{(8)}C_{(13)}$	117,8(7)
$O_{(2)}C_{(3)}C_{(10)}$	111,8(7)	$N_{(7)}C_{(8)}C_{(8a)}$	120,5(7)	$C_{(8a)}C_{(8)}C_{(13)}$	121,7(7)
$C_{(4)}C_{(3)}C_{(9)}$	109,3(7)	$C_{(8)}C_{(8a)}C_{(4a)}$	118,9(7)		

The X-ray experiment was carried out on a Hilger-Watts (UK) four circle diffractometer (MoK_α irradiation, graphite monochromator). The crystals were monoclinic: $a = 13.218(2)$, $b = 0.5309(4)$, $c = 13.671(2)$ Å, $\beta = 93.79(1)°$, $V = 1177.6(2)$ Å^3, $d_{calc} = 1.33$ gcm^3, $Z = 4$, space group $P2_1/n$. 1205 independent reflections were measured in the range $2° \leq \theta \leq 28°$ by the $\theta/2\theta$ scanning method. The structure was solved by a direct method using the MULTAN program with refinement by the least squares method in full matrix anisotropic approximation for non-hydrogen atoms. The position of all hydrogen atoms was localized in Fourier difference synthesis and included for F_{calc} with fixed positions and temperature parameters (B_{iso} = 5 Å^2). The final values of the difference factors were $R = 0.068$ and $R_w = 0.049$ from 644 reflections with $F^2 \geq 5\sigma$. All calculations were carried out on a Data General C Eclipse S/200 computer (USA) using the INEXTL program [10].

Parameters for II-XIV are given in Tables 1 and 2 and the coordinates for the non-hydrogen atoms and valence angle values in Tables 3 and 4.

5-Acyl-2,2-dimethyltetrahydropyran-4-ones (II-IV, VIII). The appropriate acid chloride (0.12 mole) was added dropwise with stirring to a solution of enamine I (19.7 g, 0.1 mole) and triethylamine (11.9 g, 0.12 mole) in dry benzene (140 ml) with the temperature maintained at 35°C. The solution was held for 1 h at 35°C, at 20-22°C for 12 h and hydrochloric acid (20%, 50 ml) was added. The product was refluxed for 30 min (reflux condenser), cooled, and the aqueous layer removed. The benzene layer was washed with water to neutrality. The aqueous layer was treated with 10% NaOH to pH 5-6 and extracted twice with benzene. The combined benzene extracts were dried ($MgSO_4$), the benzene evaporated off, and the residue distilled.

5-Aroyl-2,2-dimethyltetrahydropyran-4-ones (V-VII) were prepared similarly but the mixture was refluxed for 30 min (reflux condenser) following acid chloride addition.

1-Alkyl-6,6-dimethyl-5,6-dihydro-3-oxo-4-cyano-8H-pyrano[3,4-c]pyridines (IX-XI). Diethylamine (4.2 ml) was added to a solution of the α-acylpyran-4-one (II-IV, 0.1 mole) and cyanoacetamide (13.6 g, 0.16 mole) in ethanol (70 ml) and the mixture was left for 48 h at 20-22°C. Ethanol was evaporated off, water (50 ml) added, and the formed crystals were filtered off, washed with water, dried, and recrystallized from ethanol.

1-Aryl-6,6-dimethyl-5,6-dihydro-3-oxo-4-cyano-8H-pyrano[3,4-c]pyridines (XII-XIV) were obtained analogously from the α-aroylpyran-4-one (V-VII, 0.1 mole), cyanoacetamide (0.15 mole) and diethylamine (23 ml) with refluxing of the mixture for 6 h (reflux condenser) following the diethylamine addition.

7,7-Dimethyl-7,8-dihydro-2-oxo-4-phenyl-3-cyano-5H-pyrano[4,3-b]pyridine (XV, $C_{17}H_{16}N_2O_2$). A solution of benzylidenecyanoacetamide (1.7 g, 10 mmole) and enamine I (2 g, 10 mmole) in ethanol (25 ml) was stirred for 8 h at 50-60°C, cooled, acidified with HCl (10%) and the crystals produced filtered off, washed with ethanol and dried to give the product (0.6 g, 21%) with mp 297-298°C (from nitromethane). R_f 0.76 (ethanol–hexane, 3:1). IR spectrum: 3290 (NH), 2230 (CN), 1650 (C=O), 1600 cm^{-1} ($C=C_{arom}$). UV spectrum, λ_{max} (log ε): 243 (3.8), 277 (4.2), 348 nm (4.0). PMR spectrum (DMSO-d_6): 7.40 (5H, s, C_6H_5); 4.0 (2H, t, CH_2O); 2.60 (2H, t, CH_2); 1.2 ppm (6H, s, $2CH_3$). M^+ 280 (mass spectrometric).

1,6,6-Trimethyl-5,6-dihydro-3-chloro-4-cyano-8H-pyrano[3,4-c]pyridine (XVI, $C_{12}H_{13}ClN_2O$). A mixture of pyrano[3,4-c]pyridine IX (21.8 g, 0.1 mole) and phosphorus oxychloride (150 ml) was refluxed (condenser) for 3 h on a water bath. Excess chloride was distilled off, the residue cooled in iced water, stirred, and aqueous KOH (10%, 200 ml) added in small portions. The crystalline product was filtered off, washed with water, and dried to give the product (21.7 g, 92%) with mp 125-126°C (from methanol). R_f 0.54 (ethanol–ether, 1:3). IR spectrum: 2230 (CN), 1580 ($C=C_{arom}$), 1150 cm^{-1} (C–O–C). PMR spectrum: ($CDCl_3$): 4.70 (2H, t, CH_2O); 2.8 (2H, t, CH_3); 2.4 (3H, s, CH_3); 1.3 ppm (6H, s, $2CH_3$).

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