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SYNTHESIS OF N-AROYLPYRUVOYL- AND N-AROYLACETYL-HETARYLAMINONITRILES

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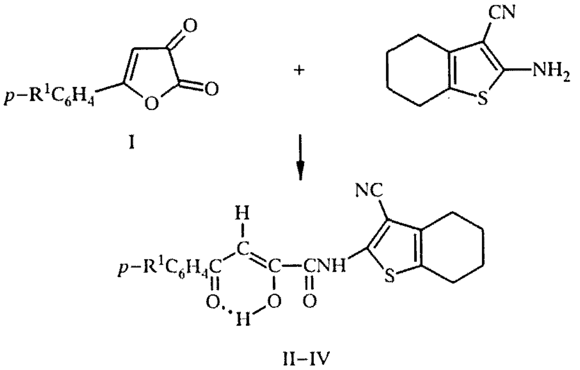
5-Aryl-2,3-dihydrofuran-2,3-diones react with five-membered hetarylaminonitriles to give N-aroylpyruvoyl and N-aroylacetyl derivatives of the latter. The reaction of 2,2-dimethyl-6-aryl-1,3-dioxin-4-ones with these hetarylaminonitriles leads solely to the N-aroylacetyl derivatives.

We previously carried out a detailed investigation of the reaction of 5-aryl-2,3-dihydrofuran-2,3-diones (I) with aliphatic and aromatic aminonitriles [1]. The reaction products were N-cyanoalkyl- or N-cyanophenyl-amides of aroylpyruvic acids, which were found to include compounds with antimicrobial and antiinflammatory activity [2]. It was of interest to study the reaction of furandiones with heterocyclic aminonitriles and study the effect of the heterocycle in the reactant on the activity of the amino and cyano groups in this reaction.

Furandiones were reacted with the following aminonitriles containing five-membered aromatic heterocycles: 2-amino-1,5-diphenylpyrrole-3,4-dicarbonitrile, 2-amino-4,5-diphenylfuran-3-carbonitrile, 2-amino-4,5-tetramethylenethiophene-3-carbonitrile, and 5-amino-1-phenylpyrazole-4-carbonitrile. The studies showed that only the aminonitrile containing a thiophene ring reacted with compounds I in a similar manner to aromatic and aliphatic aminonitriles. The reaction occurred by opening of the furandione ring at the $O-C_{(2)}$ bond by the amino group of the reactant to give 2-N-aroylpyruvoyl-4,5-tetramethylenethiophene-3-carbonitriles II-IV.



In the IR spectra of compounds II-IV there are bands due to stretching vibrations of an amide NH group at 3240-3340 cm^{-1}, an amide carbonyl group at 1690-1700 cm^{-1}, and a cyano group at 2185-2210 cm^{-1}. The intense peak at 1600-1608 cm^{-1} is due to the absorption of a hydrogen-chelated ring in the β-dicarbonyl molecular residue. In the PMR spectra, in addition to signals from the aromatic protons and the four methylene groups of the cyclohexene residue, a singlet due to a vinyl proton is also present (7.08-7.13 ppm), which provides additional evidence that compounds II-IV undergo enolization. A signal due to the proton of an enol hydroxide could not be detected in the PMR spectra of these compounds, which is probably due to broadening as a result of a high degree of exchange. The actual possibility of intramolecular cyclization involving the enol hydroxyl and the cyano group [3] in compounds II-IV to give structure A does not occur, probably because of the strong

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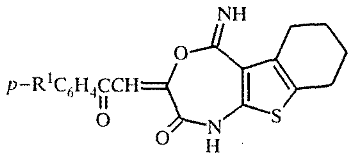
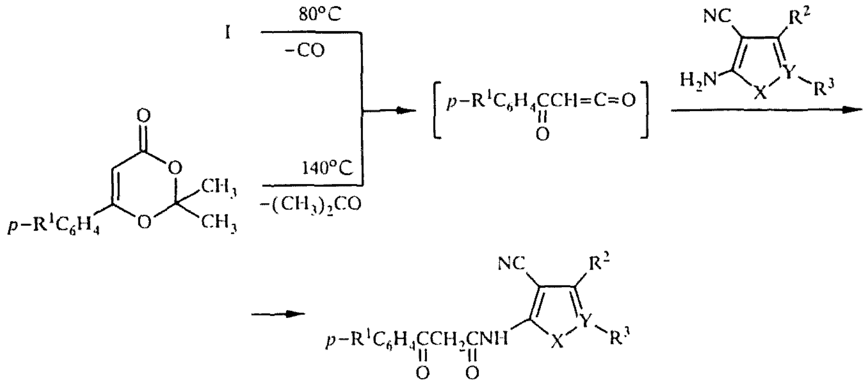
intramolecular hydrogen bond in the chelate ring [4]. The spectroscopic properties of compounds II-IV are in good agreement with the literature data [1].



A

Reaction of the hetarylaminonitriles containing furan and pyrazole rings with compounds I cause the latter to undergo decarbonylation. The resulting aroylketenes aroylacetylate the amino group of the reactant, giving the corresponding N-aroylacetylhetarylaminonitriles V-XI. 2-Amino-1,5-diphenylpyrrole-3,4-dicarbonitrile does not react with compounds I. The difference in reactivity of the above hetarylaminonitriles with the furandiones is probably due the variable nucleophilicity of the amino group, which is affected by the π-donor and π-acceptor properties of both the heterocycle itself and the substituents attached to it [5].

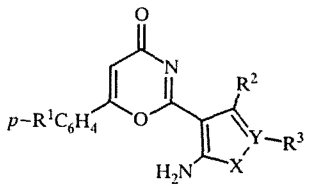


V-XIV

In the IR spectra of compounds V-XI there are bands due to the stretching vibrations of an N−H bond in the region of 3120-3260 cm^{-1} and two carbonyl groups in the region of 1660-1740 cm^{-1}. The C≡N bond has an absorption at 2210-2240 cm^{-1}. The presence of a singlet due to methylene protons at 4.06-4.23 ppm in the PMR spectra of these compounds is an indication of the β-dicarbonyl form of the aroylacetyl substituent. However, in the spectra of certain compounds (V, XI) the occurrence of signals from a methine proton with a resonance at 5.60-6.17 ppm and an enol hydroxyl at 13.08-13.20 ppm with a relative intensity of 10-12% suggests that a small amount of the tautomeric enol form is present.

In order to confirm the structure of compounds V-XI, we carried out their counter-synthesis by reaction of 2,2-dimethyl-6-aryl-1,3-dioxin-4-ones with 2-amino-4,5-diphenylfuran-3-carbonitrile and 5-amino-1-phenylpyrazole-4-carbonitrile. Because of the higher temperature for generating aroylketenes by this method (140°C) [6] it was also possible to aroylacetylate 2-amino-1,5-diphenylpyrrole-3,4-dicarbonitrile to give compound XII. N-Aroylacetyl derivatives of 2-amino-4,5-tetramethylenethiophene-3-carbonitrile (compounds XIII and XIV) were obtained by the same method.

In addition to aroylacetylation of the amino group it would be feasible for the competing reaction of [4 + 2]-cycloaddition of the aroylketenes on the cyano group of the hetarylaminonitriles [7] to occur, leading to compounds with structure B.



B

TABLE 1. Properties of N-Aroylpyruvoyl- and N-Aroylacetylhetarylaminonitriles II-XVI

Compound	Empirical formula	R^1	R^2	R^3	X	Y	mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (spin-spin coupling constant, J, Hz)*	Yield, %
1	2	3	4	5	6	7	8	9	10	11
II	$C_{19}H_{16}N_2O_3S$	H					204...205 toluene	1600, 1700, 2185, 3240	1,70and2,40 (8H, 2m cyclo-$(CH_2)_4$, 7,13 (1H, s, CH), 7,30...8,18 (5H, m, C_6H_5), 13,00 (1H, s, NH)	84
III	$C_{20}H_{18}N_2O_3S$	CH_3					182...184 toluene	1600, 1690, 2200, 3280	1,72and2,42 (8H, 2m cyclo-$(CH_2)_4$, 2,32 (3H, s, CH_3), 7,08 (1H, s, CH), 7,31; 7,91 (4H, dd, C_6H_4, $J = 9$), 11,58 (1H, s, NH)	87
IV	$C_{19}H_{15}ClN_2O_3S$	Cl					209...211 toluene	1600, 1700, 2210, 3340	1,72and2,41 (8H, 2m cyclo-$(CH_2)_4$, 7,12 (1H, s, CH), 7,32; 7,88 (4H, dd, C_6H_4, $J = 9$), 11,58 (1H, s, NH)	90
V	$C_{26}H_{18}N_2O_3$	H	C_6H_5	C_6H_5	O	C	168...170 benzene	1600, 1660, 1710, 2230, 3120, 3170	4,16 (2H, s, CH_2), 5,91 (1H, s, CH), 7,06...8,03 (15H, m, $3C_6H_5$), 11,86 (1H, s, NH), 13,15 (1H, s, OH)	73
VI	$C_{27}H_{20}N_2O_3$	CH_3	C_6H_5	C_6H_5	O	C	135...136 benzene	1590, 1660, 1730, 2210, 3130...3180	2,30 (3H, s, CH_3), 4,20 (2H, s, CH_2), 7,06...7,93 (14H, m, $2C_6H_5$, C_6H_4), 11,83 (1H, s, NH)	65
VII	$C_{26}H_{17}ClN_2O_3$	Cl	C_6H_5	C_6H_5	O	C	186...188 benzene	1600, 1660, 1740, 2220, 3170...3230	4,23 (2H, s, CH_2), 7,13...7,96 (14H, m, $2C_6H_5$, C_6H_4), 11,76 (1H, s, NH)	72
VIII	$C_{28}H_{22}N_2O_4$	C_2H_5O	C_6H_5	C_6H_5	O	C	189...190 benzene	1610, 1660, 1720, 2230, 3260	1,23 (3H, t, CH_3), 4,06 (4H, q, $2CH_2$), 6,83...8,16 (14H, m, $2C_6H_5$, C_6H_4), 11,93 (1H, s, NH)	70
IX	$C_{20}H_{16}N_4O_2$	CH_3	H	$N-C_6H_5$	N		139...142 chloroform	1620, 1690, 1710, 2245, 3225	2,26 (3H, s, CH_3), 4,13 (2H, s, CH_2), 6,03 (1H, s, CH), 7,10...7,96 (9H, m, C_6H_5, C_6H_4), 8,20 (1H, s, CH), 11,10 (1H, c, NH)	75

X	$C_{21}H_{18}N_4O_3$	C_2H_5O	H	—	N—C_6H_5	N	158...160 chloroform	1615, 1665, 1690, 2245, 3200	1,26 (3H, t, CH_3), 4,06 (4H, q, $2CH_2$), 6,83...7,93 (9H, m, C_6H_5, C_6H_4), 8,20 (1H, s, CH), 10,76 (1H, c, NH)	77
XI	$C_{19}H_{13}N_4O_2$	Cl	H	—	N—C_6H_5	N	160...162 chloroform	1600, 1680, 1710, 2240, 3210	3,83 (2H, s, CH_2), 5,6 (1H, s, CH), 7,00...7,53 (9H, m, C_6H_5, C_6H_4), 7,86 (1H, s, CH), 10,4 (1H, s, NH), 13,10 (1H, s, OH)	80
XII	$C_{28}H_{20}N_4O_2$	CH_3	CN	C_6H_5	N—C_6H_5	C	168...170 toluene	1615, 1680, 1740, 2240, 3320	2,28 (3H, s, CH_3), 4,08 (2H, s, CH_2), 7,01...7,80 (14H, m, $2C_6H_5$, C_6H_4), 10,38 (1H, s, NH)	64
XIII	$C_{18}H_{16}N_2O_2S$	H	$R^2 + R^3$ $-(CH_2)_4-$		S	C	224...225 toluene	1600, 1640, 1728, 2200, 3160	1,71and2,40 (8H, 2m cyclo-$(CH_2)_4$, 4,24 (2H, s, CH_2), 6,27 (1H, s, CH), 7,39...8,0 (5H, m, C_6H_5), 11,46 (1H, s, NH), 13,08 (1H, s, OH)	67
XIV	$C_{19}H_{18}N_2O_2S$	CH_3	$R^2 + R^3$ $-(CH_2)_4-$		S	C	214...215 toluene	1610, 1640, 1730, 2205, 3185	1,70and2,43 (8H, 2m cyclo-$(CH_2)_4$, 2,32 (3H, s, CH_3), 4,23 (2H, s, CH_2), 6,22 (1H, s, CH), 7,30, 7,82 (4H, dd, C_6H_4, $J = 8{,}2$), 11,62 (1H, s, NH), 13,31 (1H, s, OH)	69
XV	$C_{20}H_{18}N_4OS$						288...289 ethanol	1685, 2205, 3100	1,70and2,42 (8H, 2m cyclo-$(CH_2)_4$, 2,28 (3H, s, CH_3), 7,23; 7,65 (4H, dd, C_6H_4, $J = 9$), 7,12 (1H, s, 4-H-pyrazole, 10,87 (1H, s, NH), 13,87 (1H, s, NH)	96
XVI	$C_{26}H_{19}ClN_4O_2$						200...201 ethanol	1590, 1600, 1660, 2210, 3130...3420	3,75 (3H, br. signal, NH_2, NH), 4,40 (2H, s, CH_2), 7,20...7,87 (14H, m, $2C_6H_5$, C_6H_4)	98

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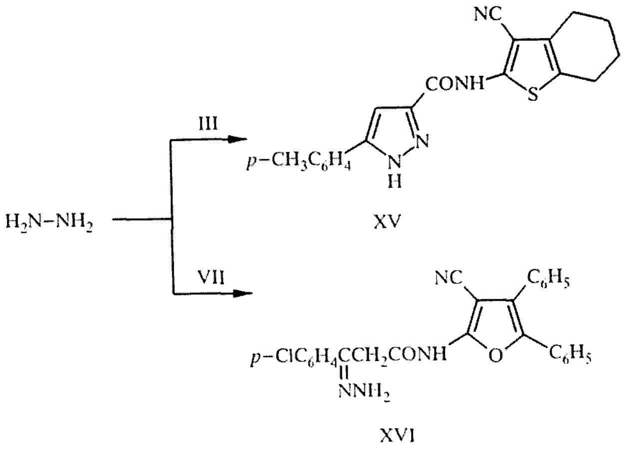
*The value of δ in ppm for cyclo-$(CH_2)_4$ were determined from the center of the multiplets; the signals due to the CH_2 protons at 2.40-2.43 ppm overlapped with the solvent signal.

However, this structure can be excluded because of the absorption of the cyano group at 2200-2240 cm^{-1} in the IR spectra of compounds V-XIV.

The presence of aroylpyruvoyl [8] or aroylacetyl substituents in the hetarylaminonitriles that were synthesized can be substantiated by their reaction with hydrazine. In the first case the β-dicarbonyl residue of compound III undergoes cyclization to a pyrazole ring, giving 2-(5-p-tolylpyrazole-3-carbamoyl)-4,5-tetramethylenethiophene-3-carbonitrile (XV), while in the second case the aroylacetyl substituent of compound VII only forms hydrazone XVI.



Screening of the hetarylaminonitriles that were synthesized on a carrageenin inflammation model did not establish that they had any superiority in antiinflammatory action compared to the medical compound orthophen.

EXPERIMENTAL

The IR spectra of compounds II-XVI were recorded on a UR-20 spectrometer in petrolatum oil. The PMR spectra for compounds II-IV and XII-XVI were recorded on a Tesla BS-587 A instrument (80 MHz), while for compounds V-XI they were recorded on a RYa-2310 instrument (60 MHz) in DMSO-d_6, with HMDS as internal standard. The purity of the compounds was determined on Silufol UV-254 plates with a benzene–ether (3:2) solvent system; iodine was used for development.

The properties of compounds II-XVI are listed in Table 1. The elemental analysis data for C, H, N, Cl, and S corresponded to the calculated values.

2-N-Aroylpyruvoyl-4-tetramethylenethiophene-3-carbonitriles (II-IV). To a solution of 0.01 mole of compound I in 15-20 ml of anhydrous dioxane was added 0.01 mole of 2-amino-4,5-tetramethylenethiophene-3-carbonitrile and the mixture was agitated for 2-3 h at 25-60°C. The precipitate that formed was filtered off and recrystallized from toluene.

2-N-Aroylacetyl-4,5-diphenylfuran-3-carbonitriles (V-VIII). **A.** To a suspension of 0.01 mole of compound I in 20-30 ml of anhydrous benzene was added 0.01 mole of 2-amino-4,5-diphenylfuran-3-carbonitrile and the mixture was boiled for 3 h. The solution was cooled an the precipitate that formed was filtered off and recrystallized from benzene. **B.** To a suspension of 0.01 mole of 2,2-dimethyl-6-aryl-1,3-dioxin-4-one in 15 ml of anhydrous o-xylene was added 0.01 mole of 2-amino-4,5-diphenylfuran-3-carbonitrile and the mixture was boiled for 15-20 min. The reaction mixture was cooled, the solvent was evaporated off, and the residue recrystallized from benzene.

2-N-Aroylacetyl-1-phenylpyrazole-4-carbonitriles (IX-XI). These compounds were obtained in a similar manner to V-VIII by methods A and B from 5-amino-1-phenylpyrazole-4-carbonitrile.

2-N-Aroylacetyl-1,5-diphenylpyrrole-3,4-dicarbonitrile (XII). To a suspension of 0.01 mole of 2,2-dimethyl-6-aryl-1,3-dioxin-4-one in 15 ml of anhydrous o-xylene was added 0.01 mole of 2-amino-1,5-diphenylpyrrole-3,4-dicarbonitrile and the mixture was boiled for 15-20 min. The reaction mixture was cooled, the solvent was evaporated off, and the residue recrystallized from toluene.

2-N-Aroylacetyl-4,5-tetramethylenethiophene-3-carbonitriles (XIII and XIV). These compounds were obtained in a similar manner to XII from 2,2-dimethyl-6-aryl-1,3-dioxin-4-one and 2-amino-4,5-tetramethylenethiophene-3-carbonitrile. They were recrystallized from toluene.

2-(p-Tolylpyrazole-3-carbamoyl)-4,5-tetramethylenethiophene-3-carbonitrile (XV). To a solution of 0.01 mole of compound III in 20 ml of ethanol was added 0.01 mole of a 50% solution of hydrazine, and the mixture was boiled for 1 h. The precipitate was filtered off.

2-N-p-Chlorobenzoylacetyl-4,5-diphenylfuran-3-carbonitrile Hydrazone (XVI). To 0.003 mole of compound VII in 30 ml of dioxane was added 0.003 mole of hydrazine hydrate in 5 ml of dioxane. The mixture was heated for 2 h, the solution was cooled, and the solvent evaporated. The precipitate was recrystallized from ethanol.

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