REACTIONS OF CYCLAMMONIUM CATIONS

XIX.* DIRECT HETARYLATION OF FURANS BY N-ACYL SALTS OF SIX-MEMBERED NITROGEN HETEROCYCLES

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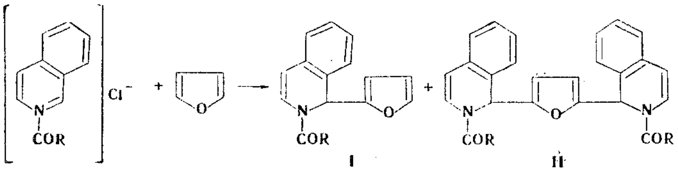
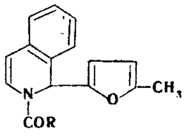
A new one-step method was found for the preparation of various heterocyclic derivatives of furans. The method consists in the reaction of six-membered nitrogen heterocycles with furans in the presence of acyl halides.

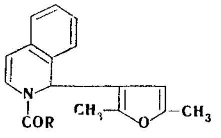
In developing the method of direct hetarylation of activated aromatic and heterocyclic rings by the action of six-membered nitrogen heterocycles in the presence of acyl halides [1-5], we have found that this route can also be used to obtain various heterocyclic furan derivatives in one step. This reaction proceeds most readily with N-acyl isoquinolinium salts, and, depending on the electronic nature of the acyl halide, mono- (I) or dihetarylfurans (II) are formed:



Thus in the reaction of furan with isoquinoline in the presence of acetyl chloride, we were able to obtain only II and traces of I ($R = CH_3$); a mixture of mono- and dihetarylfuran derivatives I and II is formed in the presence of benzoyl chloride, while we obtained only monohetarylfuran derivative I with diphenylcarbamoyl chloride, even when the reaction time was increased. This is probably explained by the different degree of electrophilicity of the N-acylisoquinolinium cations that are intermediately formed in these reactions and attack the furan ring with greater energy, the greater the electron-acceptor character of the acyl grouping attached to the nitrogen and, consequently, the greater the electrophilic properties of the cation. We have already [6,7] in principle demonstrated the possibility of transmission of the electronic effects of substituents attached to the positively charged ring nitrogen atom through this atom in pyridinium salts. Derivatives of the II type are readily formed from monoheterocyclic furan derivative I on reaction with N-acyl salts. Other α-substituted furans, for example, α-methylfuran, also react analogously with acyl salts. When both α positions of the furan are occupied, the reaction may be directed to the β position also, and in these cases only one heterocyclic residue can be introduced:



III



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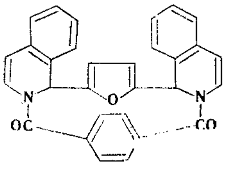

V

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*See [1] for communication XVIII.

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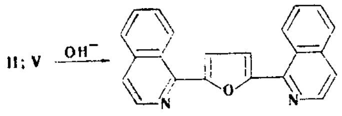
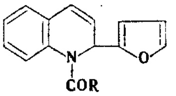
The alkaline hydrolysis of III gives 2-methyl-5-(1-isoquinolinyl)furan, the structure of which was confirmed by IR and mass spectra. The reaction with terephthalic acid dichloride gave macrocyclic system V, the hydrolysis of which gave 2,5-di(1-isoquinolinyl)furan (VI). We also obtained the same compound (VI) from the alkaline hydrolysis of dihetarylfuran II, which confirms the structure of these compounds:



VI

N-Acylquinolinium and N-acylpyridinium salts are somewhat less reactive in reactions with furan, but we were also able to obtain mono- and diheterocyclic furan derivatives in these cases:



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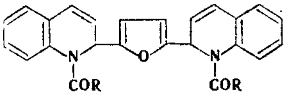

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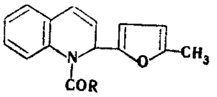

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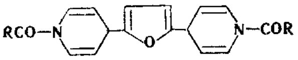
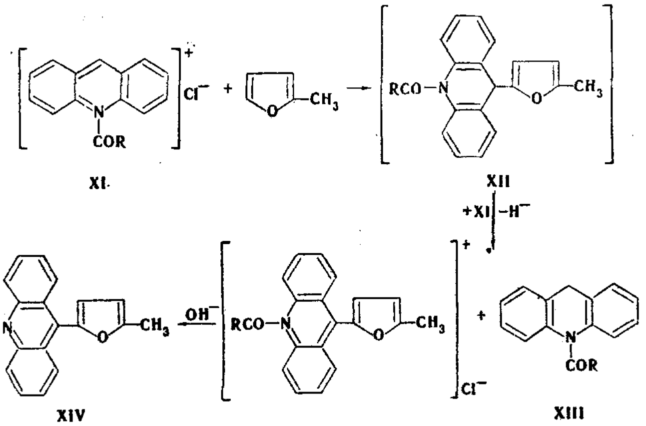


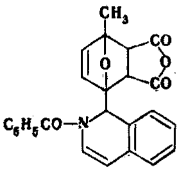
X

In the reaction of acridine with furans in the presence of acyl halides we obtained 9-substituted acridines and N-acylacridans rather than 9-substituted N-acylacridans (XII). The hydride shift that we have previously described [8] apparently occurs in this case:

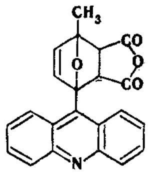


XI XII XIV XIII

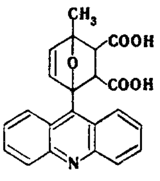
The heterocyclic furan derivatives obtained readily add maleic anhydride or maleic acid, which is characteristic for many furan derivatives [9]:



XV



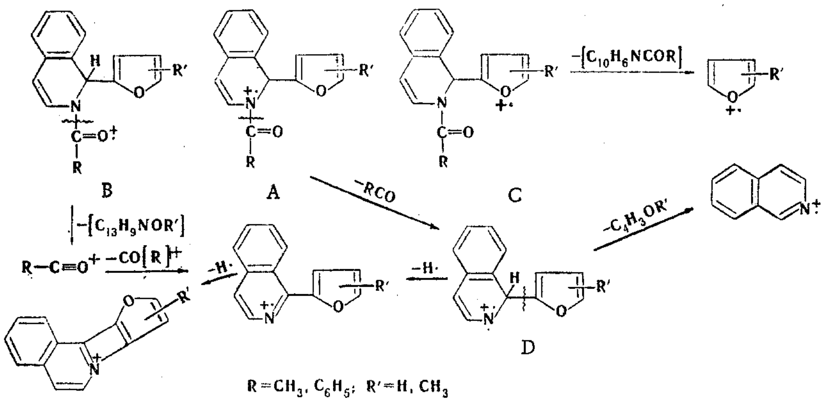
XVI



XVII

The characteristic bands of the stretching vibrations of the carbonyl group of amides at 1655-1660 cm^{-1}, of the C=C bond of the dihydroquinoline and isoquinoline rings at 1610-1620 cm^{-1}, and of the stretching vibrations of the 2-substituted furan ring at 1560-1570 cm^{-1} can be noted in the IR spectra of all of the synthesized compounds (except for the acridinylfurans). The bands that are characteristic for the stretching vibrations of the carbonyl group at 1660-1690 cm^{-1} are absent in the spectrum of acridinylfuran XIV, and a very strong band at 1695 cm^{-1} and three weak bands at 1520, 1560, and 1585 cm^{-1}, which are apparently related to the vibrations of the furan and acridine rings, were observed.

In order to confirm the structures of the synthesized compounds, we used a mass-spectrometric method of analysis. To establish the molecular weights of the samples, their mass spectra were recorded at different ionizing-electron voltages. By examining the different fragment ions in the spectra, one can establish their relationship to the proposed structure. The positive charge in the excited molecular ions of the investigated compounds can be localized on any of the three atoms that have an unshared pair of electrons (structures A, B, and C), as a consequence of which, peaks of the fragment ions, which characterize definite fragments of the molecule, should appear in the spectrum. Thus the disintegration of the investigated compounds under the influence of electron impact can be represented by the following general scheme:*



R=CH$_3$, C$_6$H$_5$; R′=H, CH$_3$

It should be noted that the charge in the molecular ion is localized primarily on the nitrogen atom of the isoquinoline ring (structure A) and on the oxygen atom of the carbonyl group (structure B). This assumption is based on the following fact: the overall contribution of disintegration processes due to structures A and B during dissociative ionization of the investigated compounds is ≥50–70% of the total ion current. This value should be considered to be sufficiently high, considering the rather low selectivity in the investigated series of compounds ($S_{1/2}$ = 6–9).

The disintegration of molecular ion A gives a peak of the $(M-RCO)^+$ fragment ion, the intensity of which is generally a maximum. Structure D, which is formed as a result of this process, disintegrates via two directions: detachment of a C_4H_3OR' radical leads to the formation of a pseudomolecular ion with an isoquinoline structure and mass 129, the further disintegration of which causes the appearance of peaks of fragment ions with masses 128 and 102 [10]; or hydrogen, initially from the α position of the isoquinoline ring, is successively eliminated, as a result of which a system consisting of two heterorings connected by a C–C bond is formed. The disintegration of similar systems was previously studied in [11, 12]. Secondary elimination of hydrogen from the α position of the furan ring leads to the formation of a stable system with condensed rings.

The disintegration of molecular ion B proceeds via a path similar to the disintegration of ketones [10, 13], where the predominant act is α cleavage relative to the carbonyl group. This process gives an intense $(M-C_{13}H_9NOR')^+$ fragment ion with subsequent splitting out of a CO molecule.

When the charge is localized on the oxygen atom of the furan ring (structure C), the C–C bond connecting the two heterorings is cleaved with simultaneous migration of a hydrogen atom from the α position of the isoquinoline ring; this process is recorded in the spectrum by the presence of the peak of the $(M-C_{10}H_6NCOR)^+$ pseudomolecular ion and a number of corresponding peaks of fragment ions that characterize the furan ring [10, 14]. The rather low intensities of the fragment ions of this process (1.5-3% of the total ion current) are due to the energetic unfavorability of cleavage of the C–C bond between the rings [11, 12, 15, 16].

Thus the presence of a molecular ion peak in the spectra of the investigated compounds and the rather intense peaks of the fragment ions of the molecular fragments confirm the structures of the synthesized compounds.

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*In most cases, the direction of the disintegration is confirmed by the presence of the corresponding metastable transition in the spectrum.

TABLE 1. Substituted N-Acyl-1,4-dihydropyridines, N-Acyl-1,2-Dihydroquinolines, and N-Acyl-1,2-dihydroisoquinolines (formulas in the text)

Comp.	R	mp, °C	R_f	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
Ia	2-Furyl	98—99[a]	0,80	$C_{18}H_{13}NO_3$	74,7	4,5	4,5	74,2	4,2	4,8	31
Ib	2-Thienyl	76—77[a]	0,90	$C_{18}H_{13}NO_2S$[c]	70,2	4,0	4,5	70,3	4,2	4,6	41
Ic	$N(C_6H_5)_2$	134,5—135,5[d]	0,50	$C_{26}H_{20}N_2O_2$	79,5	5,4	7,1	79,6	5,1	7,1	43
III	C_6H_5	87—88[a]	0,48	$C_{21}H_{17}NO_2$	79,8	5,6	4,6	80,0	5,4	4,4	41
IIa	CH_3	189—190[b]	0,20	$C_{26}H_{22}N_2O_3$	75,8	5,7	7,0	76,1	5,4	6,9	33
IIb	2-Furyl	145—146[e]	0,20	$C_{32}H_{22}N_2O_5$	74,4	4,1	5,2	74,7	4,3	5,4	31
IIc	2-Thienyl	192—193[e]	0,10	$C_{32}H_{22}N_2O_3S_2$[f]	70,0	4,5	5,0	70,3	4,0	5,1	23
V	—	160—161[e]	0,20	$C_{30}H_{20}N_2O_3$	78,3	4,2	5,8	78,7	4,4	6,1	50
VII	C_6H_5	153—154[b]	0,65	$C_{20}H_{15}NO_2$	79,3	5,2	4,9	79,7	5,0	4,6	22
IX	C_6H_5	115—116[a]	0,70	$C_{21}H_{17}NO_2$	79,9	5,5	4,2	80,0	5,4	4,4	35
VIII	C_6H_5	180—181[g]	0,10	$C_{36}H_{26}N_2O_2$	80,9	4,9	5,5	80,9	4,9	5,3	45
X	C_6H_5	185—186[h]	0,20[i]	$C_{28}H_{22}N_2O_3$	76,9	4,9	6,7	77,4	5,1	6,5	48

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[a] From methanol. [b] From ethanol. [c] Found: S 10.7%. Calculated: S 10.4%. [d] From butyl alcohol. [e] From benzene–hexane (1 : 1). [f] Found: S 11.3%. Calculated: S 11.7%. [g] From cyclohexane. [h] From ether. [i] In chloroform–benzene–hexane–methanol (30 : 6 : 1 : 1).

EXPERIMENTAL

The UV spectra of ethanol solutions were recorded with an SF-4A spectrophotometer. The IR spectra of CCl_4 solutions were recorded with a UR-20 spectrophotometer. The mass spectra were recorded with an MKh-1303 spectrometer at an ionizing electron voltage of 50 eV, a cathode emission current of 1.5 mA, an accelerating voltage of 2 kV, and an ion source and input system temperature of 250°. A benzene–hexane–chloroform system (6 : 1 : 30) was used as the eluent for chromatography in a thin layer of activity II aluminum oxide, and the spots were developed with iodine vapors and in UV light.

2-Benzoyl-1-(2-furyl)-1,2-dihydroisoquinoline (I, R = C_6H_5) and 2,5-Di(2-benzoyl-1,2-dihydro-1-isoquinolinyl)furan (II, R = C_6H_5). A mixture of 25.8 g (0.2 mole) of isoquinoline, 14.0 g (0.1 mole) of benzoyl chloride, and 6.8 g (0.1 mole) of furan in 25 ml of absolute benzene was held at room temperature for 24 h, after which the unchanged components were removed by steam distillation, and the residue in the flask was separated and dried to give 29.5 g of a mixture of I and II (R = C_6H_5). Compound I (R = C_6H_5) was isolated by repeated extraction with boiling ether to give 21.9 g (73%) of a product with mp 98-99° (from ether), R_f 0.46, and λ_{max} 300 nm (log ε 4.06). Found: C 79.5; H 5.0; N 4.7%; mol. wt. 301. $C_{20}H_{15}NO_2$. Calculated: C 79.7; H 5.0; N 4.7%; mol. wt. 301. The substance remaining after the extraction was recrystallized from cyclohexane to give 4.7 g (20%) of II (R = C_6H_5) with R_f 0.16, mp 135-136°, and λ_{max} 295 nm (log ε 4.34). Found: C 81.1; H 5.0; N 5.3%; mol. wt. 535. $C_{36}H_{26}N_2O_3$. Calculated: C 80.9; H 4.9; N 5.2%; mol. wt. 535.

Compound II (R = C_6H_5) was also obtained by the reaction of isoquinoline, benzoyl chloride, and I (R = C_6H_5) in absolute benzene at 100° for 23 h. The substance was identical to that described above, as confirmed by the absence of a melting-point depression, the results of thin-layer chromatography (TLC), and the coincidence of their IR spectra.

The other heterocyclic furan derivatives (Table 1) were similarly obtained.

2-Benzoyl-1-(2,5-dimethyl-3-furyl)-1,2-dihydroisoquinoline (IV). This compound was obtained in 70% yield by the reaction of isoquinoline, benzoyl chloride, and 2,5-dimethylfuran at 50° for 7 h and had mp 137-138° (from aqueous ethanol) and R_f 0.42. Found: C 80.0; H 5.8; N 4.6%. $C_{22}H_{19}NO_2$. Calculated: C 80.2; H 5.8; N 4.3%.

2,5-Di(1-isoquinolinyl)furan (VI). A 2.9-g sample of sodium hydroxide was added to 0.8 g of 2,5-di-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)furan in 11 ml of 70% ethanol, and the mixture was allowed to stand on a boiling-water bath for 5 h. Water (11 ml) was added, the alcohol was removed by distillation, and the precipitated material was separated, dried, and recrystallized from ethanol to give 0.4 g (83%) of a product with R_f 0.2 and mp 125-126°. Found: C 81.9; H 4.2; N 8.7%. $C_{22}H_{14}N_2O$. Calculated: C 82.0; H 4.4; N 8.7%. The picrate had mp 146-147° (from ethanol). Found: N 13.9%. $C_{22}H_{14}N_2O \cdot 2C_6H_3N_3O_7$. Calculated: N 14.2%.

2,5-Di(1-isoquinolinyl)furan was also obtained in 62% yield via a similar method by refluxing a solution of furan V and sodium hydroxide in ethanol.

2-Methyl-5-(1-isoquinolinyl)furan. This compound was obtained in 35% yield as described above by refluxing a solution of 2-benzoyl-1-(2-methyl-5-furyl)-1,2-dihydroisoquinoline and sodium hydroxide in ethanol and had mp 115-116° (from aqueous ethanol) and R_f 0.75. Found: C 80.6; H 5.2; N 6.9%. $C_{14}H_{11}NO$. Calculated: C 80.4; H 5.3; N 6.7%. The picrate had mp 148-149° (from ethanol). Found: N 12.5%. $C_{14}H_{11}NO \cdot C_6H_3N_3O_7$. Calculated: N 12.8%.

2-Methyl-5-(9-acridinyl)furan (XIV). A solution of 3.58 g (0.02 mole) of acridine, 1.4 g (0.01 mole) of benzoyl chloride, and 0.81 g (0.01 mole) of α-methylfuran in 15 ml of anhydrous benzene was heated at 90-95° for 25-27 h, after which the benzene was removed by distillation, and the residue was treated with hot water and dried to give 0.7 g (19%) of XIV with mp 104-105° (from petroleum ether) and R_f 0.6. Found: C 83.1; H 5.3; N 5.4%. $C_{18}H_{13}NO$. Calculated: C 83.4; H 5.1; N 5.4%.

Adduct of Maleic Anhydride and 2-Methyl-5-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)furan (XV). This adduct was obtained in 49% yield by heating a solution of maleic anhydride and 2-methyl-5-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)furan in absolute ether and had mp 109-110°. Found: N 3.7%. $C_{25}H_{19}NO_5$. Calculated: N 3.4%.

Adduct of Maleic Anhydride and 2-Methyl-5-(9-acridinyl)furan (XVI). This compound was similarly obtained in 29% yield and had mp 155-156°. Found: N 4.4%. $C_{22}H_{15}NO_4$. Calculated: N 4.1%.

Adduct of Maleic Acid and 2-Methyl-5-(9-acridinyl)furan (XVII). This adduct was similarly obtained in 69% yield and had mp 150-151°. Found: N 3.6%. $C_{22}H_{17}NO_5$. Calculated: N 3.8%.

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