REACTIONS OF CYCLIC AMMONIUM (CYCLAMMONIUM)

CATIONS

XV.* HETARYLATION OF PYRROLES BY N-ACYLQUINOLINIUM,

N-ACYLISOQUINOLINIUM, AND N-ACYLACRIDINIUM SALTS

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The corresponding hetarylpyrroles were obtained by the reaction of pyrroles with quinoline, isoquinoline, and acridine in the presence of acyl halides.

The reaction of six-membered nitrogen heterocycles with acyl halides gives N-acyl cyclic ammonium (cyclammonium) cations [2], which in situ are not only frequently acylating agents but also convenient electrophilic agents for the introduction of heterocyclic residues into nucleophilic aromatic [3-5] and heteroaromatic [6-10] compounds. This route was also used to obtain some heterocyclic derivatives of pyrroles [6-8] and benzopyrroles [9, 10]. These reactions, in analogy with the various reactions of carbonium ions alkylation, acylation, or tropylation - can be called hetarylation reactions.

In the present communication, we were able to demonstrate that the hetarylation of pyrroles with N-acyl cyclic ammonium cations is a general reaction and, despite the literature data [7], is possible with any N-acylquinolinium, N-acrylisoquinolinium and N-acylacridinium salts.

N-Acylisoquinolinium salts proved to be the most active salts in this reaction. The reaction of these salts with pyrroles, even at room temperature, gave high yields of mono- (I,II) and bis(2-acryl-1,2-dihydro-1-isoquinolinyl)pyrroles (III):



The ratio of the I, II, and III formed depends to a considerable degree on both the nucleophilicity of the pyrrole ring and on the electrophilicity of the N-acyl cyclic ammonium cations, which is higher the greater the electron-acceptor character of the acyl halides used in the reaction. In the reactions with N-phenylpyrrole, the nucleophilicity of which is reduced as a consequence of the electron-acceptor effect of the phenyl substituent, only one heterocyclic residue can be introduced into the α position of pyrrole. Compound III is formed predominantly with N-methylpyrrole, along with only traces of I and II, while a mixture of I, II, and III is obtained with unsubstituted pyrrole.

The N-acetyl salts are more active in these reactions than the N-benzoyl salts, while the N, N-diphenylcarbamoylisoquinolinium salt is the least active, and only I can be obtained from it.

Polyhetaryl derivatives I and II can subsequently participate in hetarylation to form III or 2.5-dihetarylpyrroles with different heterocyclic residues or identical heterocycles, which, however, have different

* See [1] for communication XIV.

Donetsk State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1654-1659, December, 1971. Original article submitted June 20, 1970.

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UDC 547.748'831'833'835



In the reaction with the acid dichloride of 4,4'-diphenyldicarboxylic acid in dilute solution we obtained macrocyclic system V, to which, on the basis of the IR spectra and in analogy with the remaining reactions, we assigned the structure of the product of the intramolecular hetarylation of pyrrole in both α positions:



Quinoline, like isoquinoline, also forms mono- and 2,5-bis(1-acyl-1,2-dihydro-2-quinolinyl)pyrroles on reaction with pyrroles in the presence of acyl halides:



In contrast to this, under similar conditions in the reaction of N-acylacridinium salts, we obtained 2,5-diacridinylpyrroles and N-acylacridane rather than N-acyl-9-pyrrolylacridanes; the same thing occurs during the acridinylation of aromatic compounds [5]:



It was found that the hetarylation of pyrroles is also possible with vinylogs of N-acyl cyclic ammonium cations formed as the active intermediates in the reaction of pyrroles with six-membered nitrogen heterocycles in the presence of β -chlorovinyl ketones, for example



The structures of XII and XIII, which we obtained by the reaction of N-acylquinolinium and isoquinolinium salts with 2,5-dimethylpyrroles, do not raise any doubts.

However, we made the assignments of the isomers of I, II, VI, and VII, which are formed in the reaction with pyrrole, and proved the structures of the products of the hetarylation of 2,4-dimethylpyrrole (XIV and XV) by means of their IR spectra. The spectra of such compounds contain a characteristic band of the

Com- pound	R	R'	mp, °C	R _j	UV spectra		tra, cm-1	Empirical	Found				Calc.				Yield,
					λ _{max} ,	lg 8	k spec N-fi,	formula	ма	%	1, %	4°.''	м	8°	1, %	1. %	90
12	C ₆ H ₅	Н	136-1385	0,68	225 265	4,83 4,83	3420	$C_{20}H_{16}N_2O$		80,0	5,7	9,2		80,0	5,4	9,3	25
IЪ	C ₆ H ₅	C ₆ H ₅	149—150 ^C	0,63	290	4,22		$C_{26}H_{20}N_2O$		82,9	5,4	7,3		82,9	5,4	7,4	88
Ic	$(C_6H_5)_2N$	н	231-232 ^d	0,89	227 297	4,45 4,28	3440	$C_{26}H_{21}N_{3}O$		80,1	5,7	11,2		79,8	5,4	10,7	58
Id	C ₆ H₅COCH=CH	н	158—159 ^e	0,19		-	3410	$C_{22}H_{18}N_2O$		81,3	5,4	8,5		81,0	5,6	8,6	60
lla	CH3	Н	182—183 ^f	0,53	224 267 288 315	4,34 4,14 4,19 4,04	3450	C ₁₅ H ₁₄ N ₂ O	268	75,8	6,0	12,2	238	75,6	5,9	11,7	71
Шb	2-Furyl	н	125—126 ^d	0,45	228 290	4,31	3470	$C_{18}H_{13}N_2O_2$	280	74,7	5,0	9,8	290	74,5	4,8	9,7	16
IIIa	C_6H_5	H	197—198 ^b	0,52	235 275	5,27 5,40	3460	$C_{36}H_{27}N_3O_2$		81,3	5,2	7,7		80,9	5,2	7,9	37
IIIb	C_6H_5	CH₃	199—200 [°]	0,39	227 281	4,56 4,50	_	$C_{37}H_{29}N_3O_2$	584	81,5	5,8	8,3	548	81,1	5,3	7,7	49
IIIf	2-Furyl	н	170—171 [°]	0,18	293	4,42		$C_{32}H_{23}N_3O_4$	518	74,6	4,6	8,2	514	74,8	4,5	8,1	14
ΙſΙd	2-Thienyl	н	184—185 ^f	0,64	233 280	4,59 4,49	3410	$C_{32}H_{23}N_3S_2O_2$	537	70,4	4,6	7,6	546	70,4	4,2	7,7	48
IIIe	CH3	Ή	263—264 ^f	0,21	228 294	4,36 4,20	3430	$C_{26}H_{23}N_{3}O_{2}$		76,1	5,4	9,9		76,3	5,7	10,3	27
IV	$C_6H_5, 2$ -]furyl	н	179—181 [°]	0,18	278	4,39	3430	$C_{34}H_{25}N_3O_3$	563	77,7	5,1	8,1	524	78,0	4,8	8,0	72
V	C_6H_4 C $_6H_4$	Н	242243 ^g	0,17	220 270	3,52 3,70	3425	$C_{36}H_{25}N_3O_2$		81,1	4,7	7,5		81,3	4,7	7,9	43
VIa	C ₆ H ₅	Н	158—160 ^d	0,50	222	4,55	3425	$C_{20}H_{16}N_2O$		79,8	5,3	9,2		80,0	5,4	9,3	30
VIb	C ₆ H ₅	C ₆ H₅	8788 ^C	0,69	228 270	4,43	-	$C_{26}H_{20}N_2O$		83,0	5,7	6,8		82,9	5,4	7,4	44
VII	C_6H_5	Н	177—178 ^d	0,66	225	4,52	3460	$C_{20}H_{16}N_2O$		79,9	5,6	9,5		80,0	5,4	9,3	40
VIIIa	C_6H_5	Н	118—119 ^d	0,38				$C_{36}H_{27}N_{3}O_{2}$		80,5	5,6	8,2		80,9	5,2	7,8	10
VIIIb	CH3	Н	204-205 ^f	0,30	234 274	4,80 4,19	3410	$C_{26}H_{23}N_{3}O_{2}$		76,0	5,7	10,3	4	76,3	5,7	10,3	25
XII a	C_6H_5	Н	149—150 [°]	0,33	294	4,23	3488	$C_{22}H_{20}N_2O$		80,2	6,4	8,3		80,4	6,1	8,5	66
XII b	C_6H_5	C ₆ H ₅	242—243 ^c	0,66	276	4,28		C ₂₈ H ₂₄ N ₂ O		83,0	5,7	6,7		83,1	5,9	6,9	67
XIII a	C ₆ H ₅	н	202—203 [°]	0,24	222	4,51		$C_{22}H_{20}N_2O$		79,8	6,3	8,8		80,4	6,1	8,5	56
XIII b	C ₆ H ₅	C ₆ H ₅	195—196 ^h	0,76	218	4,54		$C_{28}H_{24}N_2O$		83,4	5,6	7,2		83,1	5,9	6,9	36
XIV a	C ₆ H ₅	н	195—196 [°]	0,74	225	4,40	3450	C22H20N2O		80,4	6,5	8,2		80,5	6,1	8,5	43
XIVb	CH3	н	225226 ⁱ	0,33	230 227 285	4,27	3435	C ₁₇ H ₁₈ N ₂ O		77,0	6,3	10,3		76,7	6,8	10,5	42
XV	C ₆ H ₅	н	215—216 ¹	0,40	226 268	4,15 4,25	3452	$C_{22}H_{20}N_2O$		80,8	6,1	8,0		80,5	6,1	8,5	82
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 $\label{eq:TABLE 1. 2-Acyl-1-pyrrolyl-2(3)-1,2-dihydroisoquinolines and 1-Acyl-2-pyrrolyl-2(3)-1,2-dihydroquinolines and 1-Acyl-2(3)-1,2-dihydroquinolines and 1-Acyl-2(3)-1,2-dihydroquinolines and 1-Acyl-2-pyrrolyl-2(3)-1,2-dihydroquinolines and 1-Acyl-2(3)-1,2-dihydroquinolines a$

^aThe molecular weights were determined by the Rast method. ^bFrom heptane. ^cFrom ethanol. ^dFrom petroleum ether. ^eFrom isopropyl alcohol. ^fFrom butanol. ^gFrom benzene. ^hFrom methanol. ⁱFrom acetone.

stretching vibrations of the N-H bond, the position and form of which depend to a considerable degree on the structure of the compound. An intramolecular hydrogen bond (a seven-membered ring) is apparently formed in α -hetarylpyrroles I, VI, XIV, and XV (R'=H), while this sort of possibility is hindered in the β isomers of II:



In this connection, the band of the stretching vibrations of the N-H bond in the spectra of α -substituted pyrroles in CCl₄ and CHCl₃ (no difference in the spectra is detected in the crystalline state) is shifted to 3410-3430 cm⁻¹ and broadened, while the N-H band of the β isomers is extremely narrow and is found at 3460-3500 cm⁻¹ (Table 1). When the solutions are diluted considerably, its position does not change, and this excludes the formation of an intermolecular hydrogen bond.

The formation of a hydrogen bond in such compounds has virtually no effect on the position of the band of the stretching vibrations of the C=O group, since it is situated at 1665-1675 cm⁻¹ in the spectra of all of the compounds. In addition, the band of the stretching vibrations of the C=C bond in conjugation with the benzene ring that is characteristic for 1,2-dihydroquinolines is observed at 1615-1625 cm⁻¹ in the spectra of all of the compounds.

Since the 1 position of isoquinoline [9, 11], the 2 position of quinoline [4], and the 9 position of acridine [5, 7] are, as a rule, substituted in the reactions of N-acyl salts of six-membered nitrogen heterocycles, and since we established the site of fusion of the pyrrole ring by means of IR spectra, there is every basis to assign the I-VIII and XII-XV structures (Table 1) to the compounds that we obtained. On the basis of the data presented in Table 1, it is difficult to establish the principle of the substitution of the hydrogen atoms of the pyrrole ring in hetarylation reactions. We note, that, in almost all cases, we detected all three reaction products - 2-hetaryl-, 3-hetaryl-, and 2,5-dihetarylpyrroles - on the chromatograms. Only those compounds that could be isolated and purified by fractional crystallization are presented in Table 1; in some cases, we demonstrated the fundamental possibility of isolating all of the reaction products by means of preparative chromatography.

The direct introduction of a heterocyclic residue into the β position of the pyrrole ring when the α position is free is not really so unusual, although it does require additional confirmation. It was recently reported [12] that both the α and β isomers of alkylpyrroles are formed in the alkylation of pyrroles.

EXPERIMENTAL

The IR spectra of $CHCl_3$ or CCl_4 solutions $(1 \cdot 10^{-3} - 5 \cdot 10^{-3} M)$ of all of the compounds were recorded with a UR-20 spectrophotometer. The UV spectra of 96% ethanol solutions were recorded with an SF-4A spectrometer. Chromatography was carried out in a thin layer of activity II aluminum oxide with elution by benzene-hexane-chloroform (6:1:30) and development with iodine vapors.

The pyrroles used in this study were prepared by the methods presented in [13].

Reaction of Quinoline with Pyrrole in the Presence of Benzoyl Chloride. A solution of 5.9 g (0.045 mole) of quinoline, 3.17 g (0.022 mole) of benzoyl chloride, and 1.53 g (0.022 mole) of pyrrole in 6 ml of anhydrous benzene was heated at 50° for 6 h under nitrogen. The reaction mixture was then steam-distilled and the residue in the distillation flask was separated and dried to give an overall yield of 5.54 g. Preparative chromatography of this product on aluminum oxide gave three compounds: 2.08 g (30%) of 1-benzoyl-2-(2-pyrrolyl)-1,2-dihydroquinoline (VIa), 2.77 g (40%) of 1-benzoyl-2-(3-pyrrolyl)-1,2-dihydroquinoline (VII), and 0.69 g (10%) of 2,5-bis(1-benzoyl-1,2-dihydro-2-quinolinyl)pyrrole (VIIIa). The analytical data and other characteristics of these and similarly obtained compounds are presented in Table 1.

The other compounds presented in the table were obtained directly by crystallization of the reaction mixture rather than by preparative chromatography.

2,5-Diacridinyl-9-pyrrole (XI). A solution of 8.96 g (0.05 mole) of acridine, 3.52 g (0.025 mole) of benzoyl chloride, and 1.68 g (0.025 mole) of pyrrole in 20 ml of absolute benzene was held at room tempera-

ture for 24 h, after which the benzene was removed by distillation. The residue was treated with ammonium hydroxide and hot water and dried. The dried material was extracted repeatedly with boiling petroleum ether, and the insoluble residue was recrystallized from butanol to give 5.6 g (53%) of XI with mp (356-358° (mp 362-364° [7]). and R_f 0.19. Found: C 85.6; H 4.7; N 10.0%. C₃₀H₁₉N₃. Calculated: C 85.5: H 4.5: N 9.9%. Both monoacridinylpyrrole isomers were detected on the chromatogram (R_f 0.40 and 0.75), but they could not be purified.

2,4-Dimethyl-5-(9-acridinyl)pyrrole. This compound was obtained as described above in 54% yield with mp 257-259° (mp 268-269° [7]) and R_f 0.56. Found: N 10.6%. $C_{19}H_{16}N_2$. Calculated: N 10.3%.

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