PRODUCTION OF ALKANE AND CYCLOHEXANE DERIVATIVES WITH TWO HETEROCYCLIC SUBSTITUENTS OF THE FURAN, PYRROLE, AND THIOPHENE SERIES

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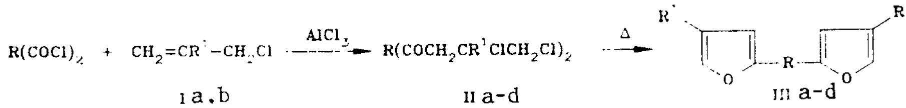
Heating 1,2,11,12-tetrachloro-2,11-bis(R-4,9-dodecanediones) and 1,4-bis(3-R-3,4-dichlorobutanoyl)cyclohexanes gave, respectively, 1,4-difuryl derivatives of butane and cyclohexane, while treatment of them with primary amines or phosphorus pentasulfide in DMF was used to synthesize dipyrryl and dithienyl compounds. 1-R-3-R^1-3,4-Dichlorobutanones react with ethylenediamine in aqueous alkali solutions to give 1,2-dipyrryl or monopyrryl derivatives of ethane.

Compounds that contain two five-membered aromatic heterorings with one heteroatom are frequently encountered among natural compounds, but not enough effort has been put into methods for synthesizing them [1].

It is known that the products of electrophilic addition of carboxylic acid chlorides to allyl and methallyl chlorides under the conditions of the Kondakov—Krapivin reaction [2] may be starting compounds for obtaining furan [3-5], pyrrole [5-7], and thiophene [5, 8] derivatives. To ascertain the limits of applicability of the method that we developed for the synthesis of five-membered heterocycles [3, 5, 6, 8] we studied the possibility of the synthesis by this method of compounds containing two five-membered aromatic heterorings with the same heteroatom of the furan, pyrrole, and thiophene series.

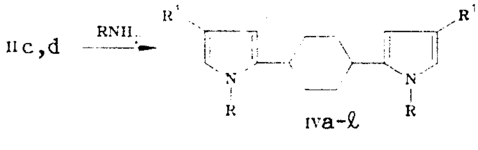
The reaction of adipic and cyclohexane-1,4-dicarboxylic acid dichlorides with allyl or methallyl chloride in the presence of aluminum chloride gives 1,2,11,12-tetrachloro-2,11-bis(R^1-dodecanedione) derivatives IIa, b and 1,4-bis(3-R^1-3,4-dichlorobutanoyl)cyclohexane derivatives IIc, d. Heating IIa-d leads to their heterocyclization to give butane 1,4-furyl derivatives IIIa, b (see Table 1) and cyclohexane derivatives IIIc, d [9]:



The structures of IIIa-d are confirmed by spectral data (Table 2) and chemical transformations. In the PMR spectra of IIIa-d one observes signals of a 1,4-bis-substituted butyl fragment at 1.4-2.9 ppm (and of a cyclohexane fragment at 1.1-2.4 ppm), as well as characteristic multiplets of protons of a furan ring at 5.65-7.2 ppm.

The furan rings in IIIa-d react with maleic anhydride to give Diels—Alder adducts [10].

We also used chloro ketones to obtain compounds containing two pyrrole fragments in their molecules. Two methods for the synthesis of such structures were developed. In the first method tetrachloro ketones IIc, d, on treatment with primary amines and their derivatives, give compounds of the 1,4-bis[2-(1-R-4-R^{1}pyrryl)]cyclohexane series IVa-*l* (Table 1).



Signals of protons of a pyrrole ring (characteristic multiplets at 5.4-6.45 ppm) and an aliphatic (alicyclic) fragment (see Table 2) are observed in the PMR spectra of bispyrroles IVa, b, d, f, j, *l*. In the IR spectra of IVa-*l* the absorption bands of the stretching vibrations of the short bonds of the pyrrole ring are found at 1495-1520 and

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TABLE 1. Characteristics of III and IV

Compound	Empirical formula	R*	Solvent	mp, °C [bp, °C (mm)]	Yield, %
IIIa**	$C_{12}H_{14}O_2$	C_4H_8		[108 ... 109 (3)]	42
IIIb***	$C_{14}H_{18}O_2$	C_4H_8		[117 ... 118 (3)]	51
IVa	$C_{20}H_{30}N_2$	i-C_3H_7	PrCH	196 ... 197	56
IVb	$C_{22}H_{34}N_2$	C_4H_9	Hexane	92 ... 94	57
IVc	$C_{20}H_{26}N_2$	$CH_2CH{=}CH_2$	EtOH	74 ... 75	52
IVd	$C_{18}H_{26}N_2O_2$	CH_2CH_2OH	Toluene	113 ... 115	30
IVe	$C_{28}H_{30}N_2$	CH_2Ph	EtOH	186 ... 187	45,5
IVf	$C_{26}H_{38}N_2$	C_6H_{11}	EtOH	255 dec.	52
IVg	$C_{22}H_{34}N_2$	i-C_3H_7	MeOH	103 ... 104	46
IVh	$C_{24}H_{38}N_2$	C_4H_9	MeOH	105 ... 106	48
IVj	$C_{22}H_{30}N_2$	$CH_2CH{=}CH_2$	EtOH	107 ... 108	47
IVk	$C_{20}H_{30}N_2O_2$	CH_2CH_2OH	EtOH	120 ... 121	41
IV*l*	$C_{28}H_{42}N_2$	C_6H_{11}	Toluene	208 dec.	36

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*For IIIa and IVa-f R^1 = H; for IIIb and IVg-*l* R^1 = CH_3.

**n_D^{20} 1.4955.

***n_D^{20} 1.4930.

TABLE 2. PMR Spectra of IIIa-d, IVa, b, d, f, j, *l**, and VIIIa-d

Compound	δ, ppm (SSCC, J, Hz)			
	3-H, 3'-H (2H, m)	5-H, 5'-H (2H, m)	R	R^1
IIIa	5,9	7,2	1,65 (4H, m); 2,58 (4H, m)	6,13 (2H, m)
IIIb	5,72**	6,94	1,4 ... 1,9 (4H, m); 2,4 ... 2,9 (4H, m)	1,85 (6H, d, J=8)
IIIc	5,85	7,2	1,1 ... 2,4 (10H, m)	6,19 (2H, m)
IIId	5,65	6,83*** (J=1,5)	1,15 ... 2,05 (10H, m)	1,0 (6H, d, J=7,5)
IVa	5,64	6,45	1,22 (12H, d, J=8,0); 4,02 (2H, m)	5,88 (2H, m)
IVb	5,65	6,3	0,74 ... 2,22 (24H, m); 3,38 (4H, t, J= =7,0, CH_2N)	5,87 (2H, m)
IVd	5,62	6,36	3,05 (2H, s); 3,18 (4H, t, J=7,0); 3,86 (4H, t, J=7,0)	5,84 (2H, m)
IVf	5,5	6,28	0,4 ... 2,27 (30H, m); 3,03 (2H, m, CHN)	5,73 (2H, m)
IVj	5,4	6,04	1,2 ... 2,0 (10H, m); 4,23 (4H, t, CH_2, J=8,0); 4,9 ... 5,5 (6H, m, $CH{=}CH_2$)	1,92 (6H, s, CH_3)
IV*l*	5,53	6,23	0,4 ... 2,0 (30H, m); 3,57 (2H, m, CHN)	1,9 (6H, s, CH_3)
VIIIa	6,71	7,86	2,1 ... 2,7 (4H, m); 3,1 ... 3,8 (4H, m)	7,18 (2H, m)
VIIIb	6,62	7,64	2,2 ... 2,6 (4H, m); 3,4 ... 3,8 (4H, m)	2,12 (6H, s, CH_3)
VIIIc	6,98	7,95	1,0 ... 2,1 (8H, m); 2,96 (2H, m)	7,21 (2H, m)
VIIId	7,12	7,92	1,0 ... 2,1 (8H, m); 2,95 (2H, m)	1,92 (6H, s, CH_3)

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*Signals of the protons of the cyclohexane fragment — multiplets at 1.0-2.5 ppm.

**Singlet.

***Quintet.

1540-1605 cm^{-1}, while in the IR spectra of IVd, k absorption bands of a hydroxy group at 3300-3500 cm^{-1} are also present.

Attempts to obtain 1,4-bis(pyrrylbutane) derivatives from tetrachlorides IIa, b led to resinification of the reaction mixtures.

In the second method dichloro ketones Va, b are treated with ethylenediamine in aqueous alkaline solutions. Primarily 1,2-bis[1-(2-R-4-R^1-pyrryl)]ethanes VIa-h are formed at a ratio of dichloro ketone Va, b and ethylenediamine of 2:1 in the presence of two equivalents of NaOH, while 1-(2-aminoethyl)-2-R-4-R^1-pyrroles VIIa-h are formed at a reagent ratio of 1:1 (see Table 3).

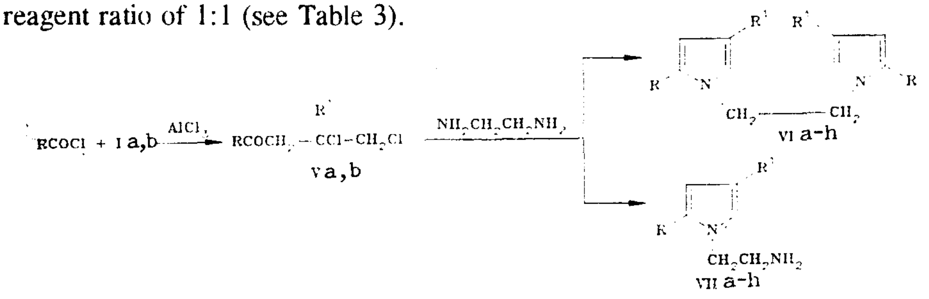

TABLE 3. Characteristics of VI-VIII

Compound	Empirical formula	R*	bp, °C (mm) [mp, °C]**	n_D^{20}	Yield, %
VIa	$C_{16}H_{24}N_2$	C_3H_7	107 ... 109 (3)	1,5155	39
VIb	$C_{16}H_{24}N_2$	i-C_3H_7	103 ... 105 (3)	1,5095	37
VIc	$C_{22}H_{32}N_2$	C_6H_{11}	[90 ... 91]	—	38
VId	$C_{24}H_{36}N_2$	2-$CH_3C_6H_{10}$	[141 ... 143]	—	32
VIe	$C_{18}H_{28}N_2$	C_3H_7	118 ... 120 (2)	1,5105	41
VIf	$C_{18}H_{28}N_2$	i-C_3H_7	113 ... 115 (2)	1,5095	43
VIg	$C_{24}H_{36}N_2$	C_6H_{11}	[128 ... 131]	—	40
VIh	$C_{26}H_{40}N_2$	2-$CH_3C_6H_{10}$	[152 ... 154]	—	36
VIIa	$C_9H_{16}N_2$	C_3H_7	92 ... 94 (5)	1,5140	65
VIIb	$C_9H_{16}N_2$	i-C_3H_7	89 ... 90 (5)	1,5110	67
VIIc	$C_{12}H_{20}N_2$	C_6H_{11}	125 ... 126 (5)	1,5295	54
VIId	$C_{13}H_{22}N_2$	2-$CH_3C_6H_{10}$	134 ... 136 (2)	1,5240	49
VIIe	$C_{10}H_{18}N_2$	C_3H_7	106 ... 108 (6)	1,5145	58
VIIf	$C_{10}H_{18}N_2$	i-C_3H_7	117 ... 119 (6)	1,5095	66
VIIg	$C_{13}H_{22}N_2$	C_6H_{11}	141 ... 143 (3)	1,5260	63
VIIh	$C_{14}H_{24}N_2$	2-$CH_3C_6H_{10}$	135 ... 137 (1)	1,5230	57
VIIIa	$C_{12}H_{14}S_2$	C_4H_8	103 ... 105 (1)	1,5720	44
VIIIb	$C_{14}H_{18}S_2$	C_4H_8	125 ... 127 (1)	1,5695	48
VIIIc	$C_{14}H_{16}S_2$	C_6H_{10}	[177 ... 178]	—	56
VIIId	$C_{16}H_{20}S_2$	C_6H_{10}	[200 ... 201]	—	58

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*VI, VIIa-d, VIIIa, c R^1 = H; VI, VIIe-h, VIIIb, d R^1 = CH_3.

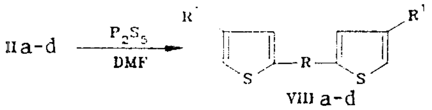
**The compounds were recrystallized: VIc, h from EtOH, and VId, g and VIIIc, d from MeOH.

TABLE 4. PMR Spectra of VIb, c, f, g and VIIb, c

Compound	δ, ppm (SSCC, J, Hz)					
	3-H, 3'-H, m	5-H, 5'-H, m	R	R^1	NCH_2CH_2N	NH_2, s
VIb	5,64 (2H)	6,28 (2H)	1,14 (12H, d, J=8,0); 2,83 (2H, m)	5,87 (2H, m)	4,08 (4H, s)	—
VIc	5,83 (2H)	6,35 (2H)	1,0 ... 2,0 (22H, m)	6,03 (2H, m)	4,07 (4H, s)	—
VIf	5,56 (2H)	6,34 (2H)	1,18 (12H, d, J=8,0); 2,91 (2H, m)	1,98 (6H, s, CH_3)	4,02 (4H, s)	—
VIg	5,8 (2H)	6,44 (2H)	0,8 ... 2,0 (22H, m)	1,86 (6H, s, CH_3)	4,0 (4H, s)	—
VIIb	5,78 (1H)	6,31 (1H)	1,18 (12H, d, J=8,0); 2,92 (2H, m)	5,92 (1H, m)	2,55 (2H, t, J=7,0); 3,46 (2H, t, J=7,0)	1,73
VIIc	5,52 (1H)	6,31 (1H)	1,0 ... 2,0 (11H, m)	5,8 (1H, m)	2,51 (2H, t, J=7,0); 3,42 (2H, t, J=7,0)	1,75

In the PMR spectra of VIb, c, f, g, in addition to the characteristic signals of the protons of five-membered rings, one observes signals of protons of a substituted ethane fragment in the form of a singlet at 4.0-4.08 ppm, while in the case of products VIIb, c these protons give signals in the form of two triplets at 2.51-2.55 and 3.42-3.46 ppm with spin-spin coupling constants (SSCC) of 7 Hz (see Table 4). The IR spectra of VIa-h contain absorption bands of stretching vibrations of the multiple bonds of a pyrrole ring at 1495-1600 cm^{-1}, whereas in the case of VIIa-h absorption bands of stretching vibrations of a primary amino group also appear at 3305-3350 and 3440-3450 cm^{-1}.

Tetrachloro ketones IIa-d react with phosphorus pentasulfide in DMF to give 1,4-bis[2-(4-R^1-thienyl)]butanes VIIIa, b and cyclohexanes VIIIc, d with yields of 44-58% (see Table 3).



VIII a-d

In the PMR spectra of VIIIa-d, in addition to the characteristic multiplets of protons of a thiophene ring at 6.62-7.12 and 7.64-7.95 ppm, one observes signals of protons of a cyclohexane fragment in the form of a multiplet at 1.0-2.1 ppm or multiplets of protons of a butane fragment at 2.1-2.7 and 3.1-3.8 ppm. The IR spectra of these compounds contain stretching vibrations of a CH group, as well as vibrations of the multiple bonds of a thiophene ring at 3040-3150 and 1500-1610 cm^{-1}.

Thus, on the basis of the products of electrophilic addition of monocarboxylic acid chlorides and dicarboxylic acid dichlorides to allyl or methallyl chloride, we have developed simple and convenient preparative methods for the synthesis for a large number of bisfuran, bispyrrole, and bisthiophene derivatives of alkanes and cyclohexane.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil or of thin layers were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in CCl_4 or $CDCl_3$ were obtained with a Tesla BS-467 spectrometer (60 MHz) with tetramethylsilane (TMS) or hexamethyldisiloxane (HMDS) as the internal standard. The purity of the reaction products was monitored by TLC on Silufol UV-254 plates.

The results of elementary analysis for C, H, N, and S for III, IV, VI, VII, and VIII were in agreement with the calculated values.

1,4-Bis(2-difuryl)butane (IIIa). A mixture of 14.7 g (0.11 mole) of aluminum chloride and 80 ml of dry dichloroethane was cooled to −20°C, after which 8.35 g (0.05 mole) of adipic acid dichloride and 9.2 g (0.12 mole) of chloride Ia were added successively, and the reaction mixture was stirred until the temperature reached room temperature. The mixture was decomposed with 5% hydrochloric acid solution, the organic layer was separated, and the aqueous layer was extracted with ether (3 × 100 ml). The combined organic extracts were washed successively with water, 10% $NaHCO_3$ solution, and water, and dried with $CaCl_2$. The solvents were removed by distillation, and the residue was distilled in vacuo in a stream of nitrogen. IR spectrum: 1517, 1598 (C=C); 880 cm^{-1} (CH).

Difuran IIIb. This compound was similarly obtained. IR spectrum: 1534, 1610 (C=C), 889 cm^{-1} (CH).

General Method for Obtaining Bispyrroles IVa-*l*. A 0.33-mole sample of the primary amine in 50 ml of ether was added at −10°C to a solution of 0.1 mole of tetrachloro diketone I in 100 ml of absolute ether, after which the mixture was refluxed for 4 h, cooled, washed successively with water, 10% Na_2CO_3 solution, water, and dried with Na_2SO_4. The solvent was removed by distillation, and the residue was recrystallized.

General Method for Obtaining VIa-h and VIIa-h. A 0.1-mole sample of dichloro ketone Va, b was added at −5°C to an aqueous solution of 0.05 mole of ethylenediamine and 0.2 mole of NaOH (method A) or 0.1 mole of ethylenediamine and 0.2 mole of NaOH (method B), after which the reaction mixture was heated for 4 h at 60-70°C, cooled, and extracted with ether (3 × 100 ml). The ether extract was washed successively with water, 10% Na_2CO_3 solution, water, and dried with Na_2SO_4. The solvent was removed by distillation, and the residue was distilled in vacuo in a stream of nitrogen. Bispyrroles VIa-h were obtained by method A, while monopyrroles VIIa-h were obtained by method B. The bispyrroles crystallized on standing and were recrystallized from methanol or ethanol.

General Method for Obtaining Bisthiophenes VIIIa-d. A 0.1-mole sample of tetrachloro diketone IIa-d was added at −5°C to a solution of 9.8 g (44 mmole) of P_2S_5 in 100 ml of DMF, after which the reaction mixture was heated for 4 h at 80-85°C, cooled, and poured into 200 ml of water. The aqueous mixture was extracted with ether (2 × 100 ml) and methylene chloride (2 × 50 ml), and the combined extracts were washed successively with water, 5% HCl solution, and water, and dried with Na_2SO_4. The solvent was removed by distillation, and the residue was fractionated in vacuo or recrystallized.

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