3-Cyano-4-(β-carboxyethyl)-2,5-dicarboxypyrrole (VI). A mixture of 0.89 g (2.9 mmole) of pyrrole IV and 12 ml of 2 N sodium hydroxide solution was refluxed for 1 h. after which it was cooled and extracted with eight 30-ml portions of ether. The extracts were dried, the solvent was removed by vacuum evaporation, and the residue was recrystallized from acetic acid containing heptane to give 0.61 g (83%) of a product with mp 270° (mp 272-273° [6]). IR spectrum: 3180 (NH), 2630 (COOH), 2245 (CN), 1730, 1680 (COOH) cm^{-1}.

3-Cyano-4-(β-carbomethoxyethyl)pyrrole (VII). A mixture of 100 mg of tricarboxylic acid VI, 2 g of sodium acetate, and 3 g of potassium acetate was heated in a stream of nitrogen at 180-190° for 10 min and at 230° for 2 min. The mixture was then cooled and dissolved in 40 ml of water. The aqueous solution was extracted with four 10-ml portions of ether, and the extracts were dried, concentrated in vacuo to a small volume, and treated with excess diazomethane. The solvent was evaporated, and the residue was chromatographed with a column (1.5 × 15 cm) filled with silica gel with elution by chloroform. The slow-moving fraction, which gave a rose coloration with Ehrlich's reagent on Silufol UV-254, was evaporated and the residue was recrystallized from benzene containing hexane to give 4.5 mg (6.5%) of a product with mp 81-81.5°. IR spectrum: 3340 (NH), 2240 (CN). 1725 CO_2CH_3) cm^{-1}. Mass spectrum, m/e (%): 178 (M^+, 30), 147 (9), 119 (35), 118 (100), 105 (53), 92 (8); m*: 126.4 (178→150), 96.3 (147→119), 71.1 (119→92). PMR spectrum, δ, ppm: 2.63 (2H, t, $CH_2CH_2CO_2CH_3$), 2.90 (2H, t, $CH_2CH_2CO_2CH_3$). 3.61 (3H, s, $CH_2CH_2COOCH_3$), 6.57 (1H, s, 7.20 (1H, s).

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NEW SYNTHESIS OF PYRROLES

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The reaction of ammonia or a primary amine with alkyl(cycloaklyl, phenyl)-β,γ-dihalopropyl ketones gives 2-, 2,4-, and 1,2- or 1.2,4-substituted pyrroles in high yields.

We have previously shown that reaction of carboxylic acid chlorides with allyl chloride in the presence of aluminum chloride gives dichloropropyl ketones, which are converted to 2-alkyl- or 2-cycloalkylfurans on vacuum distillation [1].

In the present research we have established that pyrroles are formed in the reaction of the above-indicated dichloro ketones with excess ammonia or a primary amine (in water or in water-ether). Nitrogen-unsubstituted compounds (in the case of the reaction with ammonia) were obtained in 60-70% yields, the yields of 1-phenylpyrroles reached 75%, and pyrroles with an alkyl, allyl, or cycloalkyl group in the 1 position were obtained in yields above 80%. No substantial difficulty was observed in the synthesis of 1,2-dialkylpyrroles even in the case of those with bulky substituents.

For the preparation of 2,4- or 1,2,4-substituted pyrroles we used dichloro ketones formed by reaction of the appropriate acid chloride with methallyl chloride in the presence of aluminum chloride, but we did not

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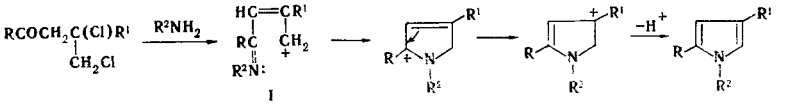
isolate them in the individual state. These ketones enabled us to obtain substances with a methyl group in the 4 position of the pyrrole ring. We were unsuccessful in an attempt to extend this method to other substituted allyl chlorides because of a considerable amount of polymerization. However, in some cases it was found to be advantageous to replace allyl chloride by the corresponding bromide. For example, we were unable to obtain any preparative yields of the desired products starting from benzoyl chloride with allyl chloride, but the reaction proceeded successfully when allyl bromide was used, and this made it possible to synthesize 2-phenylpyrrole and its 1-substituted derivatives.

Satisfactory results of elementary analysis and characteristic UV and IR spectra were obtained for the synthesized pyrroles after rectification (in vacuo, where necessary). Some of the pyrroles have been previously described, and their physical constants did not differ substantially from our values.

For example, the boiling point of 2-propylpyrrole is close to the literature value. Bands at 3392-3400 (NH), 3095 (ring C–H stretching vibrations), 1570 and 1475 (ring C–C in-plane vibrations), and 790 and 715 cm^{-1} (ring C–H deformation vibrations) are observed in its IR spectrum. In the case of the spectra of 1-substituted pyrroles, the vibrations characteristic for the pyrrole ring at 1555-1560 and 1500-1505 cm^{-1} and the absence of NH group absorption were noted. The molecular weights and the fragmentation of the molecular ion in the mass spectrum correspond to the assigned structure (the mass spectra will be the subject of a special publication). According to gas–liquid chromatography (GLC) data, the pyrroles obtained in this study contain no more than 1.5-2% impurities, mainly the corresponding furans. An examination of the PMR spectra makes it possible to assume that all of our substances have a 2-substituted pyrrole structure without a substituent in the 5 position, and this excludes possible migration of the groups during synthesis. For example, singlets of 3-H and 5-H protons of the pyrrole ring are seen in the spectrum of 2-isopropyl-2-ethyl-4-methylpyrrole at 5-34 and 6-10 ppm. A singlet at 1.94 ppm (4-H), a triplet centered at 1.14 and a quartet (2.46 ppm) of an ethyl group, and the characteristic multiplet of the isopropyl group (quartet of the CH group centered at 3.95 and doublet of methyl groups at 1.27 ppm, J = 6 Hz) are present at strong field.

We did not make a special study of the mechanism of the reaction, but it is most likely that the first step under the influence of amine is elimination of HHal, which ties up the amine and thereby prevents the possibility of polymerization. The resulting cation (I) undergoes cyclization due to intramolecular attack on the p pair of electrons of the nitrogen atom with simultaneous migration of the multiple bond. After this (or simultaneously, for otherwise attack by the cyclic cation on the neutral pyrrole molecule becomes likely), the intermediate undergoes deprotonation with aromatization.



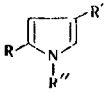
I

One should, however, allow for the simultaneous or alternative formation of an α,β-unsaturated γ-chloro ketone, which is subsequently converted to an amino ketone and cyclized. The conversion of unsaturated γ-halo ketones with similar structures to pyrroles under the influence of ammonia or primary amines has been described [2], and Rodebaugh and Cromwell [3] were even able to isolate unsaturated amino ketones in the case of cyclization of bromomethylchalcones. 1,2-Dicyclohexylpyrrole and some of its substituted derivatives were recently obtained [8] from the corresponding dichloro ketones, and it was assumed that the reaction proceeds through a step involving the formation of an aziridine.

EXPERIMENTAL

The individuality of the compounds obtained in this study was monitored by means of a Chrom-3-JKL chromatograph with PMS-100 as the mobile phase and Chromosorb W as the support. The solid compounds were monitored by chromatography on Silufol plates. The IR spectra of the compounds (without a solvent) were recorded with a UR-20 spectrometer. The PMR spectra of CCl_4 solutions of the compounds were obtained with an RS-60 or Varian T-60 spectrometer. The starting dichloro ketones were obtained via the Kondakov reaction as described in [1].

2-Methylpyrrole. A solution of 15.5 g (0.1 mole) of freshly prepared 4,5-dichloro-2-pentanone in 100 ml of ether was added dropwise with stirring while maintaining the temperature at 30-35° to a solution of 45 ml (0.6 mole) of 25% ammonium hydroxide, after which the mixture was allowed to stand at room temperature for 5 h with periodic stirring. The ether layer was then separated and washed with water, and the aqueous layer was extracted with ether. The combined extracts were dried with magnesium sulfates, the solvent was removed by distillation, and the residue was vacuum fractionated in a stream of nitrogen to give 5.6 g (69%) of 2-methyl-

TABLE 1. Substituted Pyrroles 

R	R′	R″	bp, °C (mm)	d_4^{20}	n_D^{20}	Empirical formula	Found, %			Calculated, %			Yield, %
							C	H	N	C	H	N	
C_2H_5 [a]	H	H	56—58 (13)	0,9287	1,4986	C_6H_9N							67
n-C_3H_7 [b]	H	H	59—60 (6)	0,9121	1,4908	$C_7H_{11}N$							62
Cyclopentyl	H	H	80—81 (3)	0,9374	1,4930	$C_9H_{13}N$	79,7	10,0	10,2	80,0	9,6	10,4	63
Cyclohexyl	H	H	110—112 (9)	0,9592	1,4950	$C_{10}H_{15}N$	81,0	10,4	9,2	80,6	10,1	9,4	59
CH_3 [c]	H	CH_3	41—42 (22)	0,9084	1,4925	C_6H_9N							84
C_2H_5 [d]	H	CH_3	55—56 (23)	0,9107	1,4880	$C_7H_{11}N$							79
n-C_3H_7	H	CH_3	52—53 (8)	0,8988	1,4868	$C_8H_{13}N$	77,9	11,0	11,3	78,0	10,6	11,4	74
Cyclopentyl	H	CH_3	89—90 (4)	0,9733	1,5180	$C_{10}H_{15}N$	80,7	10,3	9,2	80,5	10,1	9,4	84
Cyclohexyl	H	CH_3	90—91 (2)	0,9634	1,5185	$C_{11}H_{17}N$	81,2	10,1	8,7	81,0	10,4	8,6	80
Cyclohexyl	H	n-C_4H_9	127—128 (10)	0,9138	1,5020	$C_{14}H_{23}N$	81,6	11,2	6,9	81,9	11,2	6,8	85
Cyclopentyl	H	Cyclopentyl	mp 58—59			$C_{14}H_{21}N$	83,4	10,2	6,5	83,0	10,5	6,4	61
CH_3	H	Allyl	39—41 (4)	0,9104	1,4990	$C_8H_{11}N$	79,2	9,3	11,4	79,3	9,1	11,5	91
C_2H_5	H	Allyl	53—54 (4)	0,8976	1,4950	$C_9H_{13}N$	79,8	9,8	10,0	80,0	9,6	10,3	86
n-C_3H_7	H	Allyl	67—68 (4)	0,8908	1,4932	$C_{10}H_{15}N$	80,8	9,9	9,2	80,5	10,0	9,4	85
Cyclopentyl	H	Allyl	114—116 (12)	0,9446	1,5210	$C_{12}H_{17}N$	82,7	10,1	8,1	82,3	9,8	8,0	81
Cyclohexyl	H	Allyl	113—115 (10)	0,9414	1,5180	$C_{13}H_{19}N$	83,3	9,7	6,8	83,0	10,0	7,0	83
C_6H_5	H	Allyl	98—100 (5)	1,0412	1,5926	$C_{13}H_{13}N$	85,0	7,3	7,5	85,2	7,1	7,6	64
C_2H_5	H	C_6H_5	93—94 (6)	1,0173	1,5720	$C_{12}H_{13}N$	83,9	7,7	8,3	84,1	7,6	8,2	69
n-C_3H_7	H	C_6H_5	97—98 (4)	1,0057	1,5673	$C_{13}H_{15}N$	84,5	8,2	7,6	84,3	8,1	7,6	65
Cyclohexyl	H	C_6H_5	mp 48—49			$C_{16}H_{19}N$	83,6	10,6	6,2	83,2	10,8	6,1	60
C_2H_5	CH_3	iso-C_3H_7	48—49 (2)	0,8810	1,4742	$C_{10}H_{17}N$	78,9	11,4	9,0	79,4	11,3	9,2	81
CH_3	CH_3	Allyl	63—65 (6)	0,9001	1,4946	$C_9H_{13}N$	79,6	9,8	9,9	80,0	9,6	10,3	87
C_2H_5	CH_3	Allyl	62—63 (2)	0,8954	1,4910	$C_{10}H_{15}N$	80,2	10,2	9,1	80,5	10,1	9,4	84
CH_3 [e]	CH_3	C_6H_5	87—89 (2)	1,0240	1,5772	$C_{12}H_{13}N$							70
C_2H_5	CH_3	C_6H_5	93—94 (2)	1,0083	1,5639	$C_{13}H_{15}N$	84,9	8,0	7,3	84,3	8,1	7,5	75
Cyclohexyl	CH_3	C_6H_5	150—152 (10)	1,0972	1,5570	$C_{17}H_{21}N$	85,8	9,0	6,0	85,4	8,8	5,9	73

[a]According to [5], this compound has bp 76–77° (30 mm), d_4^{20} 0.9305, and n_D^{20} 1.5000. [b]According to [2], this compound has bp 75° (13 mm). [c]Spectral data from [6]. [d]According to [7], this compound has bp 67° (30 mm), d_4^{20} 0.9180, and n_D^{20} 1.4940. [e]According to [7], this compound has bp 97–98° (0.5 mm) and n_D^{20} 1.5800.

pyrrole with bp 60-61° (30 mm), d_4^{20} 0.9456, and n_D^{20} 1.5017. The results of analysis for C, H, and N were in agreement with the calculated values. The product was chromatographically identical to a genuine sample. According to the data in [4], this compound has bp 146-148° (749 mm), d_4^{20} 0.9438 and n_D^{20} 1.5025.

1-Isopropyl-2,4-dimethylpyrrole. A solution of 16.9 g (0.1 mole) of 4,5-dichloro-4-methyl-2-pentanone in 50 ml of ether was added dropwise at 20-25° to a solution of 18 ml (0.3 mole) of isopropylamine in 50 ml of ether, after which it was stirred at room temperature for 2 h. It was then refluxed for 3 h, cooled, washed with water, and extracted with ether. The organic layer was dried with magnesium sulfate, the solvents was removed by distillation, and the residue was vacuum fractionated in a stream of nitrogen to give 12 g (88%) of 1-isopropyl-2,4-dimethylpyrrole with bp 36-37° (2 mm), d_4^{20} 0.8886, and n_D^{20} 1.4788. Found: C 78.5; H 10.7; N 10.4%. $C_9H_{15}N$. Calculated: C 78.8; H 10.9; N 10.2%.

The other 1-alkylpyrroles were obtained in the same way (at 20-35°) (see Table 1).

1-Phenyl-2-methylpyrrole. A 15.5-g (0.1 mole) sample of 4.5-dichloro-2-pentanone was added dropwise at 30-35° to a mixture of 27 ml (0.3 mole) of aniline and 100 ml of water, after which the mixture was refluxed for 3 h and worked up as in the preceding experiments to give 11.6 g (74%) of 1-phenyl-2-methylpyrrole with bp 97-98° (9 mm), d_4^{20} 1.0341, and n_D^{20} 1.5790 [bp 112.5-113° (12 mm), d_4^{20} 1.0315, and n_D^{20} 1.5775]. The other 1-phenylpyrroles were obtained in the same way (Table 1).

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SYNTHESIS OF DERIVATIVES OF 2-BENZYLTETRAHYDROCARBAZOLE AND 4-BENZYLPYRAZINOTETRAHYDROCARBAZOLE

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2-Benzylidene- and 2-benzyltetrahydrocarbazoles were synthesized, and the latter were converted to 4-benzylpyrazinotetrahydrocarbazoles.

Up until now, only 3a.4,5,6-tetrahydropyrazino[3,2,1-jk]carbazoles with substituents only in the aromatic portion of the molecule were known [1]. For the first time we have obtained carbazoles of this sort with a benzyl substituent in the aliphatic ring for a comparison of their biological properties with those previously described. 1,2,3,4-Tetrahydro-1-oxo-2-benzylidenecarbazole derivatives (IIa-e), obtained by condensation of 1,2,3,4-tetrahydro-1-oxocarbazoles (Ia-e) with benzaldehyde in the presence of sodium methoxide or potassium hydroxide, were used as the starting compounds. Both of these catalysts ensure the synthesis of benxylidene derivatives IIa-e in high yields under mild conditions, as in the preparation of benzylidene derivatives of cyclohexanone and α-tetralone [2, 3].

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