SYNTHESIS AND PROPERTIES OF 1-ALKOXYCARBONYLMETHY-2-ALKYLPYRROLES

R. A. Gadzhily, R. A. Nadzhafova, V. G. Dzhafarov,
S. S. Asadova, and V. M. Fedoseev

The condensation of alkyl 2,3-dichloropropyl- and alkyl 2-methoxy-3-chloropropyl ketones with aminoacetic acid alkyl ester hydrochlorides leads to 1-alkoxycarbonylmethyl-2-alkylpyrroles. The reaction of these esters with various bases gives the corresponding 1-carbonylmethyl-2-alkylpyrroles, 1-dialkyl-aminocarbonylmethyl-2-alkylpyrroles, 1-carbazoylmethyl-2-alkylpyrroles, and potassium 2-alkylpyrrolyl-1-acetate.

It was shown earlier that the reaction of alkyl-2,3-dichloropropyl ketones with primary amines and their functional derivatives leads to N-substituted pyrrole derivatives [1-3]. It was established that reaction of alkyl-3-chloropropenyl ketones with hydrazine hydrate forms 1-amino-2-alkylpyrroles [4]. Experiments on the condensation of alkyl trans-2-methoxycyclopropyl ketones (products of 1,3-dehydrochlorination of alkyl 2-methoxy-3-chloropropyl ketones) with primary amines leads to N-substituted 2-alkylpyrroles [5].

In the present work we established that the reaction of alkyl 2,3-dichloropropyl- (Ia-e) or alkyl 2-methoxy-3-chloropropyl ketones (IIa-e) with alkyl aminoacetate hydrochlorides in the presence of a hydrogen chloride acceptor (triple concentration in the case of ketones I and double concentration in the case of II) leads to the formation of 1-alkoxycarbonylmethyl-2-alkylpyrroles (IIIb-d, IVa and IVc) in yields of 72-81%. The reaction proceeds in aqueous benzene at 20-25°C with subsequent boiling of the reaction mixture under reflux for 6 h [6].

The reaction of esters III and IV with ammonia, primary, and secondary amines in alcohol, dioxane, or in excess amine leads to the corresponding amide derivative. Here it was shown that the indicated esters react more readily with ammonia or primary amines than with secondary amines. Thus, for example, the reaction of compounds IIIb and IVc with ammonia easily takes place at a temperature of 35-40°C in 4 h and leads to 1-carbamoylmethyl-2-alkylpyrroles (Vb and Vc) in yields of 80 and 78%, respectively. In the case of the benzyl amine and the corresponding esters III and IV, a temperature of 50-55°C over 5 h gives the 1-benzylaminocarbonylmethyl-2-alkylpyrroles (VIa, VId) in yields of 74 and 65%. In order to complete the reaction of IIIb, IIId, IVa, and IVc with secondary amines it is necessary to keep the reaction mixture at 75-80°C for 8 h, which leads to yields of 65-82% for the 1-diethylamino- (VIIa and VIIc), 1-piperidino- (VIIIa and VIIIc) and 1-morpholinocarbonylmethyl-2-alkylpyrroles (IXb and IXd). The 1-carbazoylmethyl-2-alkylpyrroles (Xb and Xc) were synthesized in yields of 75 and 71%, respectively, by boiling the esters IIIb or IIIc for 6 h in alcohol with a small excess of hydrazine hydrate. Keeping an equimolar amount of IVb and IVe in an alcoholic solution of potassium hydroxide for 6 h at a temperature of 55-60°C gave the potassium salts of 2-alkylpyrrolyl-1-acetic acid (XIb and XIe) in yields of 85 and 78%. The treatment of salt XIb in 10% aqueous HCl solution produced the corresponding 2-alkyl-N-pyrrolylacetic acid (XIIb). The characteristics of the synthesized compounds are presented in Table 1.

The structures of the substituted pyrroles III-XII were confirmed by IR and ^1H NMR spectra. Thus, the IR spectra of these compounds showed characteristic absorption bands for the pyrrole ring at 3090-3144 ($\nu_{=C-H}$), 1485-1556 (nucleus $\nu_{C=C}$), 718-780 cm^{-1} (nucleus $\delta_{=C-H}$), and also characteristic absorption bands for the functional groups: 3280-3310 (ν_{N-H}), 1730-1750 ($\nu_{C=O}$), 1616-1672 ($\nu_{C=O}$, amide I), 1540-1637 ($\delta_{N-H\ \&\ C-N}$ amide II), 1195-1210 cm^{-1} (ν_{C-O-C}), which correspond with literature data [7].

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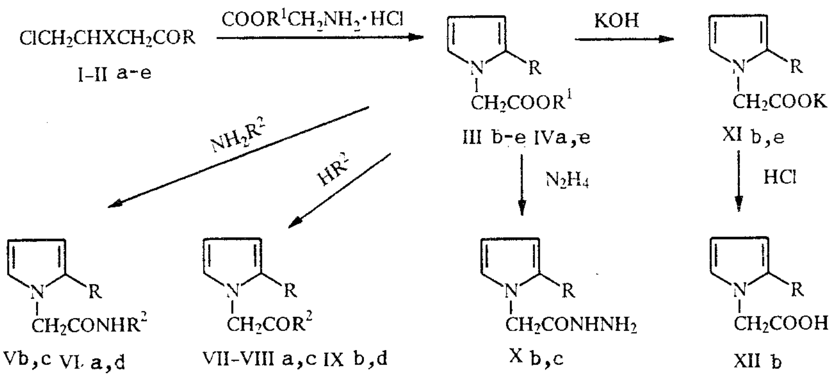
TABLE 1. Characteristics of Compounds III-XII

Compound*	Empirical formula	bp °C/mm Hg or mp, °C	Yield, %	Compound	Empirical formula	bp, °C/mm Hg or mp, °C	Yield, %
IIIb	$C_9H_{13}NO_2$	94...95/3	81	VIIc	$C_{14}H_{24}N_2O$	58...59	65
IIIc	$C_{10}H_{15}NO_2$	103...104/3	77	VIIIa	$C_{12}H_{18}N_2O$	105...106	82
IIId	$C_{12}H_{19}NO_2$	122...123/3	72	VIIIc	$C_{14}H_{22}N_2O$	83...84	74
IVa	$C_9H_{13}NO_2$	93...93/2	80	IXb	$C_{12}H_{18}N_2O_2$	104...106	79
IVc	$C_{11}H_{17}N_2O$	120...121/4	75	IXc	$C_{14}H_{22}N_2O_2$	68...69	76
Vb	$C_8H_{12}NO_2$	125...126	80	Xb	$C_8H_{13}N_3O$	118...119	75
Vc	$C_9H_{14}N_2O$	112...113	78	Xc	$C_9H_{15}N_3O$	110...111	71
VIa	$C_{14}H_{16}N_2O$	100...102	74	XIb	$C_8H_{10}NO_2K$	261...263	85
VId	$C_{17}H_{22}N_2O$	81...82	65	XIe	$C_{11}H_{16}NO_2K$	223...225	78
VIIa	$C_{12}H_{20}N_2O$	70...71	73	XIIb	$C_9H_{11}NO_2$	144...146	32

*IIIb, $n_D^{20} = 1.4907$, $d_4^{20} = 1.0489$; IIIc, $n_D^{20} = 1.4884$, $d_4^{20} = 1.0276$; IIIe, $n_D^{20} = 1.4829$, $d_4^{20} = 0.9843$; IVa, $n_D^{20} = 1.4867$, $d_4^{20} = 1.0519$; IVc, $n_D^{20} = 1.4829$, $d_4^{20} = 0.9962$.

The ^1H NMR spectra (Table 2) of the pyrroles III-XII, in addition to signals for the protons of the alkyl radicals in position 2, singlets for the protons of the $N-CH_2$ group, and three characteristic multiplets for the 3-, 4-, and 5-H of the pyrrole ring (5.50-5.80-6.90 ppm), also show signals for the protons of the functional group in the carbonylmethyl fragments.



I X = Cl, II X = OMe, I—XIIa R = Me, bR = Et, cR^3 = Pr, dR = Bu, eR = C_5H_{11}; III R^1 = Me; IV R^1 = = Et; V R^2 = H; VI R^2 = $CH_2C_6H_5$; VII R^2 = NEt_2; VIII R^2 = piperidino IX R^2 = morpholino

Thus, the described method allows the high yield, selective synthesis of the earlier unknown 1-functionally-substituted derivatives of pyrrole with defined structures.

EXPERIMENTAL

The IR spectra were recorded on UR-20 or Specord M-80 instruments as thin films or in mineral oil. The ^1H NMR spectra were obtained with a Tesla BS-487B (80 MHz) in CCl_4 or $(CD_3)_2CO$, with HMDS as internal standard. The purity of the synthesized compounds was monitored by TLC on Silufol UV-254 plates.

The starting alkyl 2,3-dichloropropyl ketones Ia-e were obtained by the electrophilic addition of carboxylic acid chlorides to allyl chloride in the presence of aluminum chloride in dichloroethane at −15°C according to [8]. The alkyl 2-methoxy-3-

TABLE 2. ^1H NMR Spectra of Compounds III-XII

Compound	Chemical shift, δ, ppm					
	3-H, s	4-H, s	5-H, s	$N-CH_2$, s	R	R^{1-7}
IIIb	5,67	5,82	6,30	4,30	1,10 t, 3,40 q	3,54 s
IVa	5,65	5,80	6,25	4,12	1,90 s	1,01 t, 4,15 q
Vc	5,60	5,76	6,43	4,30	0,85 t, 1,52 q, 2,35 t	4,73
VIa	5,62	5,83	6,42	4,38	1,94 s	4,20 d, 6,70 br.s. 7,20 s
VIIa	5,50	5,63	6,75	4,09	1,85 s	0,85 t, 2,45 q
VIIIa	5,58	5,70	6,33	4,75	1,90 s	1,40 m, 3,30 m
IXb	5,57	5,75	6,35	4,70	1,34 t, 2,63 q	2,22 t, 3,50 t
Xb	5,63	5,75	6,42	4,75	1,31 t, 2,91 q	2,81 s, 9,40 br.s
XIb	5,80	6,34	6,90	4,70	1,27 t, 2,74 q	—
XIIb	5,61	6,30	6,82	4,64	1,40 t, 2,83 q	10,6 br.s

chloropropyl ketones IIa-e were prepared by the addition of methyl alcohol to alkyl 3-chloropropyl ketones as described in [5, 9].

The elemental analysis data for compounds III-XII for C, H, and N corresponded with the calculated values.

1-Alkoxycarbonylmethyl-2-R-pyrroles (IIIb, IIIc-e, IVa, and IVc). A. To a solution of 0.1 mole of the amino acid methyl or ethyl ester hydrochloride in 50 ml of water was added successively dropwise at a temperature of 20-25°C 6 g (0.55 mole) of sodium carbonate dissolved in 50 ml of water, 0.1 mole of ketone I in 100 ml of benzene, and 28 ml (0.2 mole) of triethylamine. The reaction mixture was boiled for 6 h and after cooling, the benzene layer was separated, washed with water, the water layer was extracted with ether, the ether extract was combined with the benzene layer and dried with $MgSO_4$. After distillation of the solvent, the residue was distilled under vacuum.

B. To a solution of 0.1 mole of amino acid methyl or ethyl ester hydrochloride in 50 ml of water was added dropwise in succession at a temperature of 20-25°C 6 g (0.55 mole) of sodium carbonate dissolved in 50 ml of water, 0.1 mole of ketone II in 100 ml of benzene, and 14 ml (0.1 mole) of triethylamine. The reaction mixture was boiled for 6 h, then treated as described above for Method A for isolation of the product. The compounds III and IV obtained were identical by bp, n_D^{20}, and IR and ^1H NMR spectral data with the pyrroles obtained by Method A.

1-Carbamoylmethyl-2-alkylpyrroles (Vb, Vc). Ammonia gas was passed through a solution of pyrroles IIIb or IVe in 100 ml of methanol or ethanol to saturation at 35-40°C for 4 h. After the reaction mixture was cooled to room temperature, 100 ml of ether was added and the precipitate was filtered off, dried, and recrystallized from heptane.

1-Benzylaminocarbonylmethyl)- or (dialkylaminocarbonylmethyl)-2-alkylpyrroles (IVa, IVd, VII-VIIIa and c, IXb, and IXd). A solution of 0.05 mole of benzylamine, diethyl amine, piperidine, or morpholine and 0.05 mole of pyrroles IIIb-IIId, IVa or IVc in 50 ml of alcohol, dioxane, or excess secondary amine was kept for the case of benzylamine at 50-55°C for 5 h and for the case of secondary amines at 75-80°C for 8 h. After cooling the mixture, the crystals were washed with ether, filtered, dried, and recrystallized from heptane.

1-Carbazoylmethyl-2-alkylpyrrols (Xb, Xc). To a solution of 6 ml (0.06 mole) of hydrazine hydrate in 25 ml of methanol or ethanol was added dropwise 0.05 mole of pyrrole IIIb or IIIc dissolved in 25 ml of ethyl alcohol. The reaction mixture was boiled under reflux for 6 h and cooled. The crystals were washed with ether, filtered off, dried, and recrystallized from heptane.

Potassium 2-Alkylpyrrole-1-acetates (XIb, XIe). To a solution of 0.05 mole of potassium hydroxide in 100 ml of methyl or ethyl alcohol at 55-60°C was added dropwise with stirring 0.05 mole of pyrrole IIIb or IIIe in 25 ml of alcohol. The reaction mixture was then stirred at the same temperature for 6 h. After cooling, 2/3 of the alcohol was distilled under vacuum, 100 ml of ether was added to the residue, and the resulting crystals were filtered off, washed with ether, and dried.

2-Ethyl-N-pyrrolylacetic Acid (XIIb). To a solution of 0.05 mole of potassium salt XIb in 25 ml of water was dropwise added 20 ml of 10% HCl at a temperature of 20-25°C. The reaction mixture was extracted with methylene chloride, the extract was washed with water, and dried with $MgSO_4$. After concentration of the solution, the resulting crystalline residue was recrystallized from methanol.

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