cluding H-6,7,9), 8.07 (1H, dd, J_{7H-9H} = 1.9, J_{6H-7H} = 6.9 Hz, 7-H), 8.26 (1H, d, J = 1.9, 9-H), 8.88 ppm (1H, d, J = 6.9 Hz, 6-H). Found, %: Cl 8.0. $C_{23}H_{25}ClN_2O_4$. Calculated, %: Cl 8.3.

10,10-Dimethyl-8-phenyl-10H-pyrido[1,2-α]indole Perchlorate (IIIc). A solution of Ia (5.87 g, 30 mmole) and cinnamaldehyde (3.96 g, 30 mmole) in acetonitrile (15 ml) was heated for 3 h at 75°C, cooled to 20°C, and alcohol (8 ml) followed by 60% $HClO_4$ (3.33 g, 20 mmole) were added. The mixture was kept at 0°C for 48 h, the crystalline product filtered off, and recrystallized from acetonitrile to give 1.5 g (13%) with mp 222-223°C. PMR Spectrum (CD_3CN): 1.79 (6H, s, 10,10-CH_3), 7.56-8.26 (9H, m, Ar excluding H-6,7,9), 8.34 (1H, dd, J_{7H-9H} = 1.9, J_{6H-7H} = 6.8 Hz, 7-H), 8.56 (1H, d, J = 1.9 Hz, 9-H), 9.31 ppm (1H, d, J = 6.8 Hz, 6-H). Found, %: C 64.5, H 4.8, Cl 9.5. $C_{20}H_{18}ClNO_4$. Calculated, %: C 64.6, H 4.9, Cl 9.5.

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CONVERSION OF 5-HYDROXY TO 5-AMINO AND 5-ALKOXYPYRAZOLIDINES

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1-Acyl-5-hydroxypyrazolidines readily exchange their hydroxyl group when treated with primary amines or alcohols to form the corresponding 5-amino or 5-alkoxypyrazolidines. An acid catalyst is needed for the preparaton of the 5-alkoxypyrazolidines.

We have previously shown that 1-acyl-5-hydroxypyrazolidines (obtained by condensation of alkenals with β-alkyl(aryl)hydrazides [1] readily exchange their hydroxyl group in reactions with hydrazines or hydroxylamines to form compounds in the linear β-hydrazinohydrazone (oxime) or cyclic (pyrazolidine) forms [2]. This work concerns the reaction of 5-hydroxypyrazolidines with other nucleophiles (amines and alcohols).

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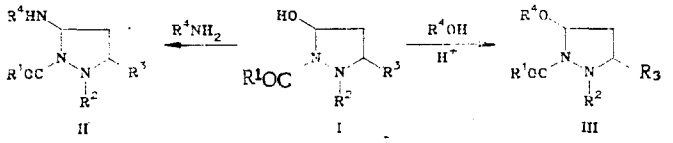
TABLE 1. 5-Amino and 5-Alkoxypyrazolidines

Compound	R^3	R^4	mp, °C	Found, %		Calculated, %		Yield, %
				C	H (N)	C	H (N)	
IIa	H	C_6H_5	149—150	72,8	6,9	72,6	6,8	70
IIb	H	p-CH_3—C_6H_4	180—182	72,9	7,3	73,2	7,1	69
IIc	H	p-Br—C_6H_4	200—203	56,9	5,2	56,7	5,0	75
IId	H	p-CH_3O—C_6H_4	147—148	67,3	6,6	67,3	6,5	67
IIe	H	p-NO_2—C_6H_4	260(decomp.)	—	(17,2)	—	(17,2)	54
IIf	H	$C_6H_5CH_2$	74—76	73,2	7,2	73,2	7,1	76
IIg	H	*cyclo*-C_6H_{11}	80—82	71,5	8,9	71,2	8,8	80
IIh	CH_3	C_6H_5	173—174	73,4	7,4	73,2	7,1	64
IIi	CH_3	p-Br—C_6H_4	206—208	57,8	5,4	57,8	5,4	70
IIj	CH_3	*cyclo*-C_6H_{11}	73—74	71,9	9,1	71,8	9,0	84
IIk	H	p-NO_2—C_6H_4	220(decomp.)	57,2	6,8	57,5	6,9	90
IIIa	H	CH_3	84—85	66,3	7,7	65,5	7,3	70
IIIb	H	C_2H_5	73—74	67,0	7,3	66,7	7,7	76
IIIc	H	C_3H_7	64—65	67,7	8,0	67,7	8,1	55
IIId	H	*iso*-C_3H_7	67—68	67,8	8,3	67,7	8,1	67
IIIe	H	$C_6H_5CH_2$	86—87	73,0	6,7	73,0	6,8	68
IIIf	CH_3	C_3H_7	55—56	68,7	8,8	68,7	8,4	74
IIIg	CH_3	*iso*-C_3H_7	59—60	69,2	8,9	68,7	8,4	59
IIIh	CH_3	CH_3	Oil	67,6	8,4	67,8	8,1	70

*IIa-k, IIIa-g $R^1 = CH_3$, IIIh $R^1 = C_2H_5$, IIa-j, IIIa-h $R^2 = C_6H_5$, IIk R^2 = iso-C_3H_7.

Substitution of amino for hydroxyl in 1-acyl-5-hydroxypyrazolidines (I) occurs readily without catalysis both for aliphatic (benzylamine, cyclohexylamine) and for aromatic primary amines to form the corresponding 5-amino derivatives IIa-k (Table 1):



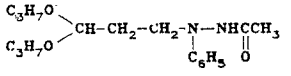
II I III

I a $R^1=CH_3$, $R^2=C_6H_5$; b $R^1=R^3=CH_3$, $R^2=C_6H_5$; c $R^1=CH_3$, R^2=*iso*-C_3H_7; d $R^1=C_2H_5$, $R^2=CH_3$, $R^3=C_6H_5$

With secondary aliphatic amines (diethylamine, piperidine) and with the sterically hindered tert-butylamine this reaction did not occur. Attempts to use acid catalysis (p-toluenesulfonic acid, Ku-2 ion exchange resin in the H^+ form) to accelerate the reaction did not lead to any kind of change. According to the PMR spectroscopic data in Table 2 all of the aminopyrazolidines II (in contrast to the 5-hydrazinopyrazolidines [2]) existed only in the cyclic form. The primary indication was the presence of the H-5 signal at 5.2-6.3 ppm and the absence of an "aldehydic" proton at 9-10 ppm. In the aliphatic amino derivatives IIf,g the 5-H appeared as a double doublet ($J_{45} = J_{4'5} = 6$ Hz) and the signals for 3-H were separate multiplets (3.34 and 3.80 ppm for IIf and 3.12 and 3.60 ppm for IIg).

Substitution of the hydroxyl group in I by alkoxy with the use of alcohols necessitated acid catalysis (HCl, Ku-2 ion exchange resin in the H^+ form) and led to good yields of 5-alkoxypyrazolidines III (Table 1). Use of the solid Ku-2 acid catalyst was preferred because it simplified and accelerated workup of the reaction mixture increasing the yields. The absence of potential hydrogen bonds in the 5-alkoxy derivatives led to a shift of the infrared carbonyl absorption band (1680-1685 cm^{-1}) when compared with the 5-hydroxy and 5-amino analogs (1640-1650 cm^{-1}). According to PMR spectral data the 5-amino and 5-alkoxy derivatives IIh-j and IIIf-h, like the starting 5-hydroxypyrazolidine Ib [3], exist only as a single pair of diastereoisomers.

Treatment of 5-hydroxypyrazolidine Ia with propyl alcohol gave both the alkoxypyrazolidine IIIc (55%) and the open chain acetal IV (15%).



IV

TABLE 2. PMR Spectra of 5-Amino and 5-Alkoxypyrazolidines

Compound	Solvent	PMR spectrum, δ, ppm (Hz)						
		3-H, m	4-H, m	5-H	R^1, s	R^2, m	R^3, d	R^4
IIa	$CDCl_3$	3,75	2,48	6,16 m	2,06	6,75—7,30	—	—
IIb	$CDCl_3$	3,60	2,50	6,18 m	2,02	6,70—7,30	—	2,24 s
IIc	DMSO-d_6	3,72	2,14	5,88 m	1,98	6,70—7,32	—	—
IId	$CDCl_3$	3,54	2,45	6,08 m	2,08	6,80—7,22	—	3,70 s
IIe	$(CD_3)_2CO$	3,78	2,50	5,95 m	1,96	6,72—8,10	—	—
IIf	$CDCl_3$	3,32; 3,80	2,30	5,38 d.d. (6)	2,02	6,80—7,24	—	3,86 s
IIg	$CDCl_3$	3,12; 3,60	2,10	5,26 d.d. (6)	1,90	6,60—7,18	—	2,56 m; 0,7—1,8 m
IIh*	$CDCl_3$	4,12	2,15	6,20 m	1,98	6,60—7,18	1,30 (6)	—
IIi	$CDCl_3$	4,12	2,10	6,08 m	1,96	6,60—7,25	1,30 (7)	—
IIj	$CDCl_3$	2,75	2,20	5,44 m	2,00	6,74—7,28	1,23 (7)	1,2—2.3 m
IIk	DMF-d_7	2,90	2,25	5,91 d.d. (7, 4)	2,05	0,94 d (6); 3,30 m	—	7,0—7,2 m 7,8—8,0 m
IIIa	CCl_4	3,56	2,15	5,60 d.d. (6)	1,98	6,75—7,25	—	3,36 s
IIIb	CCl_4	3,58	2,20	5,72 d.d.(6)	1,98	6,70—7,25	—	1,10 t (7)
IIIc	CCl_4	3,55	2,20	5,66 d.d (6)	2,00	6,70—7,20	—	0,8 t (8); 1,5 m 3,5 m
IIId	CCl_4	3,54	2,16	5,82 d.d.(6)	2,00	6,74—7,28	—	0,98 d (6); 1,3 d; 4.0 s
IIIe	CCl_4	3,60	2,19	5,88 d.d.(5)	2,01	6,90—7,30	—	4,70 s
IIIf	CCl_4	4,00	2,25	5,70 d.d.(7)	1,98	6,78—7,24	1,23 (6)	0,88 t (8); 1,5 m 3,5 m
IIIg	CCl_4	4,06	2,16	5,85 d,d(7)	1,99	6,76—7,24	1,02 (6)	1,25 t (6); 4.06 m
IIIh	CCl_4	4,15	2,20	5,83 d.d. (4, 6)	1,1 t; 2,4 q (8)	6,90—7,40	1.28 (7)	3,57 s

*NH Proton chemical shifts were: IIh 3.60 br s; IIi 3.60 d ($J_{NH,5H}$ = 9 Hz); IIj 4.10 br s; for IIa-g the signal occurred in the aromatic proton region.

The evidence for this acetal was derived from the presence of an NH infrared absorption band at 3210 cm^{-1}, and both the absence of a 5-H proton signal at 5-6 ppm and presence of a double intensity propyl signal in the PMR spectrum. Thus the high activity of the hydroxyl group in the substitution reactions of 5-hydroxypyrazolidines permits the preparation of 5-alkoxy and 5-aminopyrazolidines (which can show interest as bioactive substances). According to preliminary data,* compounds IIIb and IIa,b show notable antiinflammatory activity although inferior to that of the starting material Ia [1].

EXPERIMENTAL

IR Spectra were recorded on a UR-20 instrument for vaseline mulls and PMR spectra on Bruker 250 and Tesla BS-497 (100 MHz) equipment using TMS as internal standard. TLC reaction control and purity were derived using Silufol UV-254 plates and benzene—ethyl acetate (1:1) eluant.

The starting 1-acyl-5-hydroxypyrazolidines (Ia-d) were prepared by [1]. Yields and physicochemical parameters are given in Tables 1 and 2.

1-Acetyl-5-aminopyrazolidines (IIa-k). A mixture of 1-acetyl-5-hydroxypyrazolidines (Ia-c, 5 mmole) and the primary amine (5 mmole) was refluxed in benzene (20 ml) for 2-5 h (IIk for 2 h at 20°C) and the reaction was monitored by TLC. After removal of solvent in vacuo, the residue was filtered and recrystallized from benzene (IIa-d), acetonitrile (IIe,k), or a mixture of benzene:hexane (IIg,h,j). If solvent evaporation failed to give a solid, the product was triturated with hexane.

1-Acetyl-5-alkoxypyrazolidines (IIIa-g). Ku-2 ion exchange resin (H^+ form, 0.1 g) was added to a solution of starting 1-acetyl-5-hydroxypyrazolidine (5 mmole) in the corresponding alcohol (10 ml) (for benzyl alcohol the reaction was carried out in acetonitrile using an equimolar amount of alcohol). The mixture was stirred until disappearance of starting pyrazoli-

*Experiments carried out in the Pharmacology Department of the Leningrad Pharmaceutical Chemistry Institute (Director: Professor L. V. Pastushenkov).

dine, tar filtered off and the filtrate evaporated in vacuo. Chromatography of the residue on silica gel (40 × 100 μ) with benzene:ethyl acetate (1:1) gave a fraction with R_f 0.6-0.8 on silufol and this was recrystallized from a mixture of benzene–ether or by vacuum distillation.

5-Methoxy-2-phenyl-3-methyl-1-propionylpyrazolidine (IIIh). Four drops of HCl were added to a solution of 5-hydroxy-2-phenyl-3-methyl-1-propionylpyrazolidine (Id, 0.3 g, 1.2 mmole) in a mixture of methanol (5 ml) and water (2 ml). After a day the solution was neutralized (Na_2CO_3), extracted with chloroform (3 × 5 ml) and separated chromatographically on silica gel (40 × 100 μ) in chloroform. Removal of solvent by distillation gave a viscous oil.

Acetic Acid β-phenyl-β-(3,3-dipropoxypropyl)hydrazide (IV). Ku-2 exchange resin (H^+ form, 0.1g) was added to a solution of 1-acetyl-2-phenyl-5-hydroxypyrazolidine (Ia, 1.03 g) in propanol (10 ml) was stirred at 20°C for 4 h. Filtration of tar, evaporation of alcohol, and chromatography of the mixture (silica gel, 40 × 100 μ, eluant benzene–ethyl acetate 1:1) gave two fractions with R_f 0.74 (IIIc) and 0.48 (IV) on silufol. Evaporation of solvent from the second fraction gave a white solid which was recrystallized from benzene–hexane (4:1) to give IV (0.15 g, 15%) with mp 64-65°C. IR Spectrum: 3210 (NH), 1690 cm^{-1} (CO). PMR spectrum ($CDCl_3$): 0.92 (6H, t, J = 7 Hz, $\underline{CH_3}CH_2CH_2O$), 1.60 (4H, m, $CH_3\underline{CH_2}CH_2O$), 1.98 (2H, m, $(C_3H_7)_2CH\underline{CH_2}$), 2.02 (3H, s, CH_3CO), 3.24 (6H, m, CH_2O, CH_2N), 4.58 (1H, m, OCH), 6.8-7.3 ppm (5H, m, $C_6\underline{H_5}$). Found, %: C 66.2, H 9.2. $C_{17}H_{28}N_2O_3$. Calculated, %: C 66.2, H 9.1.

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SYNTHESIS OF INDOLES FROM PYRIDINIUM SALTS

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The detailed analysis of the products of the interaction of nitropyridinium salts with ketones and alkylamines resulted in new data testifying in favor of the previously proposed scheme for the formation of indoles from pyridinium salts.

The electron-deficient pyridine nucleus and, to a still greater degree, the 1-alkylpyridinium ring readily undergo ring opening by nucleophiles giving derivatives of glutaconic dialdehyde which may be utilized for the synthesis of carbo- and heterocycles; this occurs by way of an example in the enamine rearrangement [1]. The opening of the pyridine ring after addition of the nucleophile evidently proceeds by an electrocyclic mechanism [2]. There are also known examples where the derivatives of pyridine form bicyclic adducts with bidentate nucleophiles [3], or the products of their transformation [4]. With the exception of the Haner synthesis of azulenes, no conversions of pyridinium salts to new rings by the action of nucleophiles have been described [5, 6].

We established [7] that the condensation of the ketone (II) (or its enamine) with the pyridine nucleus occurs in regard to the action of substituted ketones and alkylamines on the 1-tropyridinium salts (Ia-f). This is evidently followed by the ring opening with the simulta

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