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Abstract

Full Text

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ON SOME SUBSTITUTION REACTIONS IN THE 1,2-DIHYDROPYRROLIZINE SERIES

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Until recently, compounds of the 1,2-dihydropyrrolizine series remained almost unstudied. With the appearance of an accessible method for their preparation ([1]), it became possible to investigate certain substitution reactions in these bicyclic systems.

The present communication concerns the introduction into the system of 1,2-dihydropyrrolizine and its homologs of formyl, acetyl, oxymethyl, and *N*-disubstituted aminomethyl groups. Formylation is readily carried out by the action on 1,2-dihydropyrrolizines of dimethylformamide and phosphorus oxychloride; aldehyde yields are 60–70%. Less satisfactorily (yields about 30%) proceeds the acetylation of similar heterocycles with acetic anhydride. Oxymethylation of 1,2-dihydropyrrolizines occurs on their interaction with aqueous formaldehyde in the presence of potash. The yields reach 67%.

1,2-Dihydropyrrolizines (I) are structurally close to N,α-alkyl-substituted pyrroles (II). This circumstance makes possible the occurrence of many

(II) (I)

substitution reactions in the 1,2-dihydropyrrolizine series just as in pyrroles, i.e., predominantly at position 5. Owing to the positive induction effect of the fatty chain, the electron density in their pyrrole portion is increased in comparison with pyrrole ([2]), and substitution reactions should proceed more readily. Experimental proof of the fact that substituents enter the 5-position of 1,2-dihydropyrrolizines was achieved by the method of convergent synthesis. (See the scheme of transformations.)

$$\text{(III)} \xrightarrow[POCl_3]{HCON(CH_3)_2} \text{(IV)} \xrightarrow{H_2N-NH_2} \text{(V)} \xrightarrow{C_2H_5ONa}$$

$$\text{(VI)} \xleftarrow[-H_2O]{Al_2O_3,\ ThO_2} \text{(VII)}$$

The identity of VI, obtained by two different methods, follows from comparison of their physical constants and infrared spectra (Fig. 1)*.

The point of entry of the oxymethyl group was proved by comparing the constants of a substance obtained by two different routes: from 3-methyl-1,2-dihydropyrrolizine (III) and 3-methyl-5-formyl-1,2-dihydropyrrolizine (IV).

* The authors express their gratitude to V. V. Tarasov for taking the IR spectra.

This unambiguously settles the question of substitution in the reactions of oxymethylation and acylation (formylation).

$$\text{III} \xrightarrow[K_2CO_3]{CH_2O} \text{(VIII)} \leftarrow \text{IV}$$

The Mannich reaction in the 1,2-dihydropyrrolizine series proceeds successfully. On the basis of the foregoing and by analogy with pyrrole ([3]), it should be assumed that substitution in this case also occurs in the 5-position.

By the acylation method, aldehydes (A) and ketones (B) were obtained. By the oxymethylation method, primary alcohols (C) were obtained, and by the Mannich reaction, *N*-disubstituted aminomethyl derivatives (D) of 1,2-dihydropyrrolizines were obtained (see Table 1).

A

[structural formula], where $R = H$ (IX); $R = CH_3$ (IV)

B

[structural formula] [structural formula (XI)], where $R = CH_3$ (X)

C

[structural formula] [structural formula (XVI)], where $R = H,\ R' = H$ (XII); $R = H,\ R' = CH_3$ (VIII); $R = H,\ R' = CH_2{-}CH(CH_3)_2$ (XIII); $R = C_2H_5,\ R' = CH_3$ (XIV); $R = CH(CH_3)_2,\ R' = CH_3$ (XV).

[structural formula] [structural formula (XIX)], where $R = H$ (XVII); $R = CH_3$ (XVIII).

[structural formula], where $n = 1,\ X = CH_2$ (XX); $n = 2,\ X = CH_2$ (XXI); $n = 1,\ X = O$ (XXII).

Experimental Part*

The starting 1,2-dihydropyrrolizines were obtained as described earlier ([1]). The methods for obtaining their derivatives are illustrated below by examples.

3-Methyl-5-formyl-1,2-dihydropyrrolizine (IV). Into a 0.5-liter flask are placed 68 ml of dimethylformamide and, with cooling, over 20 min 20 ml of phosphorus oxychloride are added; then at 10°, a solution of 24.24 g of (III) in 24 ml of dimethylformamide is introduced dropwise. Stirring is continued for another 30 min, and then the reaction mixture is kept at 35° for 1 hr. Into the flask are introduced 120 g of ice, and with stirring are added

* With the participation of A. A. Khorkina and V. I. Simontsev.

Table 1

Most important physical properties and analyses of derivatives of 1,2-dihydropyrrolizines obtained by substitution methods

Compound no.	B.p. (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	Gross formula	C, % found	C, % calc.	H, % found	H, % calc.	N, % found	N, % calc.	Yield, %
IV	96 – 97 (4 mm)	1.5712	1.0845	45.21	42.38	$C_9H_{11}NO$	72.36	72.45	7.35	7.44	9.34	9.39	71.7
VIII	112 (4 mm)	1.5405	1.0790	44.00	43.89	$C_9H_{13}NO$	71.07	71.54	8.80	8.67	9.11	9.26	58.8
IX	108 – 109 (4.5 mm)	1.5902	1.1325	40.29	37.76	C_8H_9NO	71.12	71.08	7.18	7.71	10.42	10.36	60.1
X	123 (10 mm)	1.5525	1.0606	49.21	46.99	$C_{10}H_{13}NO$	73.10	73.58	8.31	8.02	8.34	8.58	38.0
XI	131 – 132 (2 mm)	1.5622	1.0851	60.77	58.65	$C_{13}H_{17}NO$	76.90	76.81	8.72	8.43	6.92	6.89	31.2

Compound no.	B.p. (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	Gross formula	C, % found	C, % calc.	H, % found	H, % calc.	N, % found	N, % calc.	Yield, %
XII	116.5 – 117 (3.5 mm)	1.5532	1.1185	39.26	39.28	$C_8H_{11}NO$	70.04	70.07	8.08	8.08	10.04	10.21	55.5
XIII	118 – 120 (1 mm)	1.5187	1.0142	57.81	57.75	$C_{12}H_{13}NO_2$	74.23	74.44	9.92	9.85	7.28	7.25	56.2
XIV	129 (4 mm)	1.5220	1.0231	53.43	53.13	$C_{11}H_{13}NO_2$	73.87	73.72	9.80	9.76	8.24	8.81	50.0
XV	119 – 122 (2 mm)	1.5195	1.0131	57.95	57.75	$C_{12}H_{15}NO_2$	74.00	74.56	9.46	9.53	7.28	7.25	66.6
XVI	140 – 146 (2 mm)	1.5538	1.1035	55.53	55.55	$C_{12}H_{15}NO_2S$	69.07	69.55	7.30	7.89	7.28	7.32	42.1
XVII	98 – 99 (8 mm)	1.5150	0.9712	51.00	50.93	$C_{10}H_{13}NO_2$	73.35	73.19	9.91	9.70	8.82	8.96	68.6
XVIII	104 – 106 (10 mm)	1.5080	0.9526	55.78	55.54	$C_{11}H_{15}NO_2$	74.10	74.24	10.42	10.18	16.23	15.76	62.54
XIX	148 – 150 (10 mm)	1.5272	0.9933	67.59	67.20	$C_{14}H_{17}NO_2$	77.26	76.78	10.12	10.24	12.68	12.46	70.1

Figure 1. 1 –spectrum of VI obtained from III; 2 –spectrum of VI obtained from VII

Figure 1: Figure 1. 1 –spectrum of VI obtained from III; 2 –spectrum of VI obtained from VII

Compound no.	B.p. (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	Gross formula	C, % found	C, % calc.	H, % found	H, % calc.	N, % found	N, % calc.	Yield, %
XX	112 – 113 (5 mm)	1.5260	0.9898	67.71	67.20	$C_{14}H_{22}N_2$	76.87	77.03	10.15	10.16	12.81	12.83	75.5
XXI	140 – 141 (2 mm)	1.5288	1.9972	71.84	71.82	$C_{15}H_{24}N_2$	77.65	77.53	10.70	10.45	12.04	12.06	60.1
XXII	156 – 158 (10 mm)	1.5285	1.0540	64.42	64.22	$C_{13}H_{20}N_2O$	70.52	70.87	9.05	9.15	12.67	12.71	61.2

solution of 88 g of sodium hydroxide in 245 ml of water. The oil is extracted with ether and dried with magnesium sulfate. 5-Formyl-1,2-dihydropyrrolizine (IX) was obtained analogously.

3,5-Dimethyl-1,2-dihydropyrrolizine (VI).
a) The hydrazone (V), obtained by heating 24 g of 85% hydrazine hydrate with 10 g of (IV) in 25 ml of methanol at 60–70°, is reduced according to Kishner ([4]) in the presence of sodium ethylate in ethylene glycol medium. The reaction product is extracted with ether; the ether extracts are washed with 5% sulfuric acid, water, and alkali, and dried over solid KOH. 5.13 g of (VI) was obtained, yield 56.6%. B.p. 79–80° (10 mm), d_4^{20} 0.9612, n_D^{20} 1.5139.

Fig. 1. 1 –spectrum of VI obtained from III; 2 –spectrum of VI obtained from VII

b) For purposes of comparison, VI, obtained by the previously described method ([1]), was additionally purified with a 5% sulfuric acid solution, as described above. B.p. 79° (10 mm), d_4^{20} 0.9592, n_D^{20} 1.5136.

3-Methyl-5-oxymethyl-1,2-dihydropyrrolizine (VIII).
a) A solution of 15.7 g of (IV) in 70 ml of absolute alcohol is placed in an autoclave. Hydrogenation is carried out over Raney nickel at 30-40°. 11.5 g (72.2%) of VIII was obtained. B.p. 103-104° (2.5 mm), d_4^{20} 1.0786, n_D^{20} 1.5403.

b) Obtained by method ([5]).

Analogously, 5-oxymethyl- (XII), 1-ethyl-3-methyl-5-oxymethyl- (XIV), 1-isopropyl-3-methyl-5-oxymethyl- (XV), 3-isobutyl-5-oxymethyl- (XIII), and 2,3-tetramethylene-5-oxymethyl-1,2-dihydropyrrolizines (XVI) were synthesized.

3-Methyl-5-acetyl-1,2-dihydropyrrolizine (X).
A mixture of 8 g of 3-methyl-1,2-dihydropyrrolizine, 5 g of fused sodium acetate, and 27 g of acetic anhydride is heated at 140° for 4 h. 2,3-Tetramethylene-5-acetyl-1,2-dihydropyrrolizine (XI) was obtained analogously.

2,3-Tetramethylene-5-dimethylaminomethyl-1,2-dihydropyrrolizine (XIX).
To 6 g of 2,3-tetramethylene-1,2-dihydropyrrolizine, with stirring, a solution of 3.2 g of dimethylamine hydrochloride in 3.25 g of 35% formalin is added dropwise over 20 min. The mixture is stirred for 3 h and then treated with 15 ml of a 25% NaOH solution. The separated oil is extracted with ether; the extracts are washed with 20 ml of water and dried with calcined sodium sulfate (XIX). Analogously, 5-dimethylaminomethyl- (XVII), 3-methyl-5-dimethylaminomethyl- (XVIII), 3-methyl-5-(N-piperidinomethyl)- (XX), 3-methyl-5-(N-morpholinomethyl)- (XXII), and 3-methyl-5-(N-hexamethyleneiminomethyl)-1,2-dihydropyrrolizines (XXI) were obtained.

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Note: Figure translations are in progress. See original paper for figures.