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RESEARCHES ON 1-AZABICYCLIC COMPOUNDS

V. Acylation of 1, 2-Dihydropyrrolizines*

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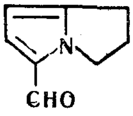
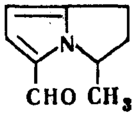
Further research on a substitution reaction of 1, 2-dihydropyrrolizines shows that they can readily be formylated with dimethylformamide in $POCl_3$; acetylation can be effected by treatment with acetic anhydride. The UV and IR spectra, and some other physical properties of 1, 2-dihydropyrrolizine aldehydes and ketones prepared for the first time are investigated.

We previously showed that 1, 2-dihydropyrrolizines readily undergo hydroxymethylation [1], and that with aliphatic and cyclic secondary amines they give the corresponding Mannich bases [2, 3]. It was also shown experimentally [3, 4] that in formylation and hydroxymethylation substitution occurs at ring position 5 (corresponding to the α-position in the pyrrole ring). All this indicates similarity of reaction between 1, 2-dihydropyrrolizines and N-alkyl-substituted pyrroles, conditioned by their structural similarity.

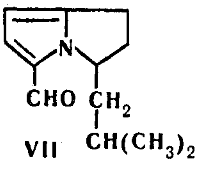
Continuing the above-mentioned systematic researches on substitution in 1, 2-dihydropyrrolizines, their formylation and acetylation has been studied. Experiments showed that 1, 2-dihydropyrrolizines are readily formylated by the Wilsmeyer method, using dimethylformamide and phosphorus oxychloride. Starting from 1, 2-dihydropyrrolizine (I), 3-methyl-1, 2-dihydropyrrolizine (II), 3-isobutyl-1, 2-dihydropyrrolizine (III), 2, 3-tetramethylene-1, 2-dihydropyrrolizine (IV), the following aldehydes were synthesized in 55-71% yield: 5-formyl-1, 2-dihydropyrrolizine (V), 3-methyl-5-formyl-1, 2-dihydropyrrolizine (VI), 3-isobutyl-5-formyl-1, 2-dihydropyrrolizine (VII), 5-formyl-2, 3-tetramethylene-1, 2-dihydropyrrolizine (VIII).



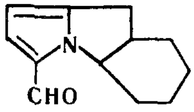
V



VI



VII

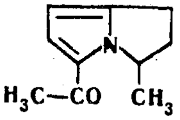


VIII

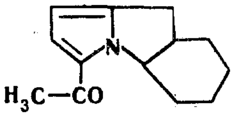
Compounds V, VI, and VII are almost colorless, rather viscous liquids, with a pleasant odor. Aldehyde VIII is crystalline, and repeated crystallization separated it into two isomers, melting points 109-111° and 48-50°.

It can be assumed that the isomerization of the aldehyde VIII arises through different positions (cis and trans) of the hydrogen atoms at the carbon atoms common to the cyclohexane and dihydropyrrolizine rings. The isomers have sharply different melting points, and give different semicarbazones. Preliminary results obtained in a PMR** spectra study of these compounds, make it possible to assume that the aldehyde with mp 48-50° is the cis form, and that the one with mp 109-111° is the trans form.

We acetylated the 1, 2-dihydropyrrolizines with acetic anhydride in the presence of sodium acetate. The dihydropyrrolizines II and IV gave respectively 3-methyl-5-acetyl-1, 2-dihydropyrrolizine (IX) and 5-acetyl-2, 3-tetramethylene-1, 2-dihydropyrrolizine (X), which were viscous, almost colorless liquids.



IX



X

The most important physical constants, along with the analyses of the compounds (V-X) which we have synthesized for the first time as well as of derivatives of them, are given in Table 1.

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* For Part IV see [13].

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Compound No.	Bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Formula	Found, %			Calculated, %			Semicarbazone				Yield, %
				Found	Calculated		C	H	N	C	H	N	Mp, °C	Formula	N, %		
															Found	Calculated	
V	108—109 (4. 5)	1.1325	1.5902	40.29	37.76	C_8H_9NO	71.12 71.00	7.18 7.17	10.42 10.24	71.08	6.71	10.36	211—212	$C_9H_{12}N_4O$	29.41 29.33	29.15	60.1
VI	96—97 (4)	1.0845	1.5712	45.21	42.38	$C_9H_{11}NO$	72.35 72.15	7.35 7.54	9.34 9.41	72.45	7.43	9.39	208—209	$C_{10}H_{14}N_4O$	27.17 27.46	27.17	71.7
VII	128.5—129.5 (5)	1.0179	1.5408	59.03	56.23	$C_{12}H_{17}NO$	75.33 75.07	9.44 9.28	7.71 7.44	75.35	8.95	7.32	204—205	$C_{13}H_{20}N_4O$	22.59 22.89	22.56	55.2
VIII	Trans-, mp 109—111	—	—	—	—	$C_{12}H_{15}NO$	75.94 75.96	8.20 8.05	7.44 7.67	76.16	7.99	7.40	200—201	$C_{13}H_{18}N_4O$	23.08 22.97	22.75	68.6
	cis-, mp . 48—50	—	—	—	—	$C_{12}H_{15}NO$	76.21 76.19	7.97 7.99	7.62 7.25	76.16	7.99	7.40	164,5—166	$C_{13}H_{18}N_4O$	22.53 22.61	22.75	68.6
IX	123 (10)	1.0606	1.5525	49.21	46.99	$C_{10}H_{13}NO$	73.41 73.58	8.31 8.29	8.34 9.04	73.58	8.02	8.58	205—206	$C_{11}H_{16}N_4O$	25.2 25.32	25.44	38.0
X	131—132 (2)	1.0851	1.5622	60.77	58.65	$C_{13}H_{17}NO$	76.90 76.74	8.72 8.50	6.92 6.94	71.81	8.43	6.89	199—202	$C_{14}H_{20}N_4O$	21.57	21.52	31.2

The UV spectra of 1, 2-dihydropyrrolizidine aldehydes and ketones are characterized by an intense peak at 299 mμ and an inflection in the 255–260 mμ region, the intensity position for these bands being preserved independent of the substituent at position 3 in the dihydropyrrolizine system (Table 2).

Table 2

Absorption Peaks in the UV Spectra of Carbonyl Compounds and Their Semicarbazones (in Methanol).

Compound number	λ_{max}, mμ	lg ε	Semicarbazones	
			λ_{max}, mμ	lg ε
V	299	4.42	311	4.49
VI	299	4.33	312	4.53
VII	299	4.48	312	4.50
VIII trans-	296	4.43	315	4.45
cis-	297	4.53	313	4.53
IX	299	4.37	306	4.49
X	297	4.37	302	4.48

The following bands are observed in the IR spectra of carbonyl derivatives of 1, 2-dihydropyrrolizines: those corresponding to C=C valence vibrations at 1545 and 1578 cm^{-1}, which are in agreement with results for pyrrole compounds [5], and intense ones in the 1035–1060 and 1290 cm^{-1} regions, probably due to vibrations of the skeleton of the dihydropyrrolizine ring, and also observed in the IR spectra of Mannich bases of 1, 2-dihydropyrrolizines [2].

The following attracts attention when investigating the physical properties of the compounds prepared. If 1, 2-dihydropyrrolizines [6] show quite satisfactory agreement between MR_D found and that calculated (the atomic refraction of nitrogen in tertiary amines is assumed), the aldehydes and ketones in this group exhibit significant and quite regular exaltation of the molecular refraction, of the order of 2.2–2.8 ml/mole (Table 1). A similar situation is found with other five-membered heterocyclic rings (furan, thiopene), and also with benzene compounds, though the values of εMR_D are different for each series of compounds when similar unsaturated groups are introduced into the ring [7].

Thus investigation of the molecular refraction gives the relative polarizabilities of different rings of aromatic character [8]. Obviously the pyrrole ring (in N-alkyl-substituted pyrroles) exhibits this property in the highest degree.

Experimental

Basically, known methods [9, 10 (method a), 11 (method b)] were used to introduce the formyl group.

Method a resembled that used previously by us [3, 4] to synthesize 3-methyl-5-formyl-1, 2-dihydropyrrolizine (VI). The product yield was 71.7%. Aldehydes V and VIII were synthesized similarly, the yields being respectively 51.9 and 66.5%.

Method b. 3-Methyl-5-formyl-1, 2-dihydropyrrolizine (VI). A 0.5 *l* flask was fitted with a stirrer, reflux condenser, and dropping funnel, then charged with 13.9 g dimethylformamide, and 29.3 g $POCl_3$ dropped in, with stirring and cooling, over 10 min. The ice bath was then removed, the mixture stirred for a further 15 min, and then 45 ml dichloroethane added with cooling. When the contents of the flask had dropped to 5°, 21 g 3-methyl-1, 2, -dihydropyrrolizine in 45 ml dichloroethane was added in 1 hr. The reaction products were stirred for 20 min, then refluxed on a water bath for 15 min, and afterwards brought to room temperature. A solution of 130 g NaOAc in 180 ml water was added, at first carefully, then rapidly, then the mixture was refluxed for 15 min, and cooled to room temperature. The organic layer which came out was separated off, and the aqueous phase extracted thrice with 40 ml ether each time. The bulked ether extracts and dichloroethane solution were washed with saturated Na_2CO_3 solution, then dried over Na_2CO_3. The solvents were distilled off, and the residue vacuum-distilled, to give 17.4 g (67.3%) aldehyde VI, which formed a colorless liquid.

Compounds V, VII, and VIII were prepared similarly in yields of 60.1, 55.2, and 68.6% respectively.

High yields of the semicarbazones of aldehydes V–VIII were prepared in the usual way [12], by treating them with semicarbazide hydrochloride and NaOAc in aqueous solution. Crystallization from EtOH gave colorless products.

3-Methyl-5-acetyl-1, 2-dihydropyrrolizine (IX). A mixture of 8 g 3-methyl-1, 2-dihydropyrrolizine, 5 g fused NaOAc, and 27 g Ac_2O was heated at 140° for 4 hr. Then the NaOAc was filtered off with suction, on a porous filter, the filtrate diluted with 40 ml Et_2O filtered, the Et_2O distilled off, and the residue vacuum-distilled, to give 4.1 g

(38%) compound IX, as a colorless liquid. Ketone X was prepared similarly.

The semicarbazones were prepared as described above. The semicarbazone of ketone X melted over rather a wide range, and possibly this is bound up with isomerization of the compound X. However so far it has not been possible to separate isomers by repeated recrystallization.

The PMR spectrum of compound VIII was measured with a high-resolution YaMR-KGU-1 type YaMR spectrometer, at a frequency of 24.342 MHz. A SF-4 spectrophotometer was used to measure the UV spectra of the aldehydes and ketones in dry MeOH at concentrations of 10^{-4}–10^{-2} mole/*l*, and with a layer thickness of 1 cm. The IR spectra were measured with an H-800 (Hilger) double beam spectrometer over the range 700–1800 cm^{-1}, using a NaCl prism. The compounds measured were pure liquids confined in the form of a capillary-thin layer between NaCl plates. The UV and IR spectra were measured by A. D. Peshekhonova.

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