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FORMATION OF SALTS FROM ACETYL- AND FORMYLPYRROLES, AND PYRROLE RING REACTIVITY

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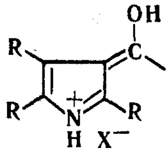
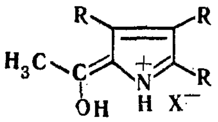
With 2-acetyl- and 2-formylpyrrole, salt formation is via proton addition to the carbonyl oxygen. In salt formation with pyrrole derivatives having an acetyl or formyl group at position 2, position 5 is deactivated for electrophilic substitution. With salts of 3-acetyl- and 3-formylpyrroles, position 2 is also deactivated, while position 5 is activated.

The oxygen atom of the acetyl group in β-acetylpyrroles has enhanced electron density, and in salt formation, protonation occurs at that atom, giving structure I [1]. Obviously with α-acetylpyrroles salt formation must proceed similarly, with formation of structure II, since a marked shift of carbonyl absorption frequency towards lower frequencies (table, bases 1 and 2) indicates a considerable shift of the unshared pair of electrons of the nitrogen atom of the pyrrole ring towards the oxygen of the acetyl group. The electron density of the pyrrole group in formyl aldehydes (table, bases 3-5) is also enhanced (lowering of C=O frequency in comparison with a normal keto group frequency of ~ 1715 cm^{-1}), so structure III can be expected to be formed through salt formation.


I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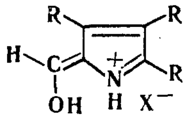
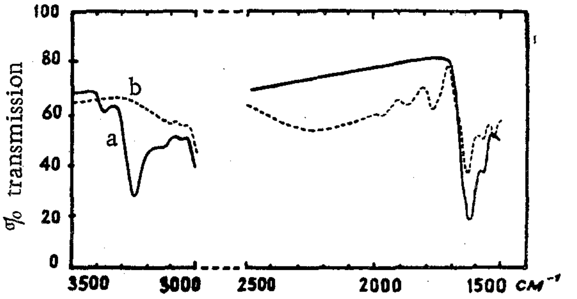
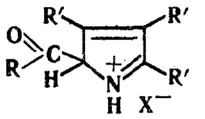

III

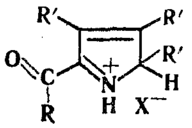
The IR spectra of α-acetyl- and α-formylpyrroles in vaseline are very similar in the 1600-2500 and 3000-3500 cm^{-1} regions to the spectra of salts of β-acetylpyrroles (cm^{-1}). Characteristic of all of them is disappearance of sharp N-H absorption bands in the 3200-3400 cm^{-1} region, and appearance of the wide absorption of associated hydroxyl in that region. Appearance of a characteristic sharp band at about 1800 cm^{-1}, and of a wide band with a center about 2200-2300 cm^{-1}, as well, in the case of aldehydes, of less intense bands at about 1900 and 2000 cm^{-1}, is connected with absorption by the $\diagdown\!\!=NH^{+}$ group.

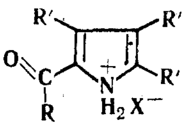


Typical IR spectrum of an α-pyrrolaldehyde (table, No. 3) in vaseline: a) base; b) hydrochloride.

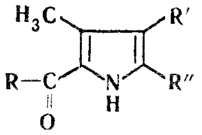
It is a fundamental point of difference between the spectra of α- and β-carbonyl pyrroles that the C=O absorption band at ~ 1620 cm^{-1}, which in the case of β-acetylpyrroles vanished [1], does not vanish in salt formation from pyrrole derivatives with an α-carbonyl group, but is shifted by ~ 10 cm^{-1} in the higher frequency direction. Obviously these bands in base and salt spectrum are due to absorption by different groups. The lower frequency of the absorption band of C=O (~ 1620 cm^{-1}) in α-acetyl- and α-formylpyrroles is due to displacement of the unshared pair of electrons of the ring nitrogen atom to the carbonyl oxygen. If it is assumed that proton addition to acetyl- and formylpyrroles occurs in such a way that a carbonyl group remains in the salt (structures IV, V, or VI formed) then in these cases the C=O absorption band must occur not at 1620-1630 cm^{-1}, but at ~ 1715 cm^{-1}, i.e., in the region of normal


IV


V


VI

Physicochemical Constants of Compounds



· p HCl

Compound number	Compound			Hydrochloride										Base		Reference
				Mp, °C	IR spectrum				Formula	Found, %		Calculated, %		IR spectrum		
	R	R′	R″		—OH	N—H	C=O	Ring vibrations		N	Cl	N	Cl	N—H	C=O	
1	CH_3	H	CH_3	151—153	3270—3000	1767 2200 (wide)	—	1623	$C_8H_{11}NO \cdot HCl$	8.03	20.49	8.07	20.42	3144 3237 3275	1614	6
2	CH_3	—CH_2—*	CH_3	245—246	3300—3000	1760 2000—2400	— —	1617	$C_{17}H_{22}N_2O_2 \cdot$ $\cdot 2HCl$	7.54	19.65	7.80	19.73	3275	1605	7
3	H	C_2H_5	CH_3	124—125	3300—3000	1766 1875 1965 2260 (wide)	—	1631	$C_9H_{13}NO \cdot HCl$	7.58	18.79	7.46	18.89	3250	1622	8
4	H	$CH_2CH_2CO_2H$	H	134—136	3300—3000	1787 1879 1956 2100 (wide) 2200 (wide)	1709 (COOH)	1623	$C_9H_{11}NO_3 \cdot HCl$	6.57	16.35	6.43	16.29	3312	1612 1727 (COOH)	9
5	H	$CH_2CH_2CO_2H$	CH_3	148—149	3280—3000	1768 1875 1938 2260 (wide)	1700 (COOH)	1633, 1648	$C_{10}H_{13}NO_3 \cdot$ $\cdot HCl$	6.21	15.16	6.05	15.31	3250 3370	1648 1714 (COOH)	10

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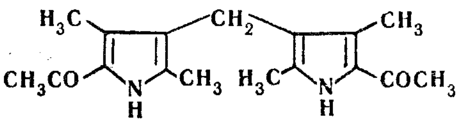
* Compound corresponds to the formula  · 2HCl

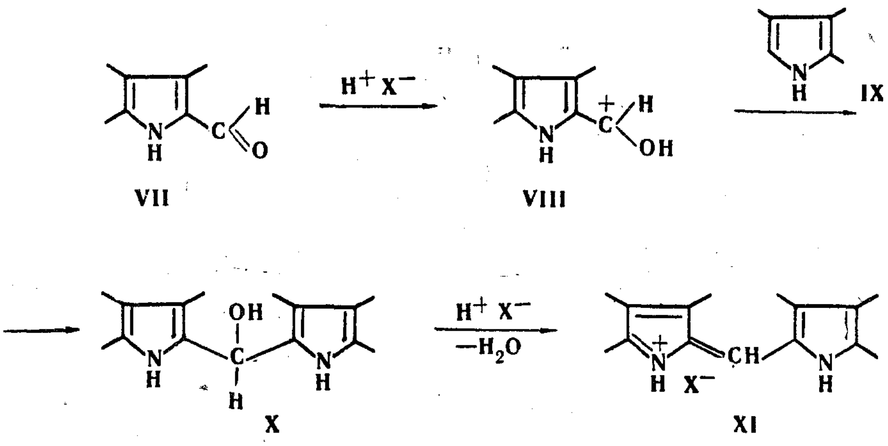
carbonyl absorption, since there is no shift of electrons from nitrogen to oxygen. The lack of a band in that region in the spectra of the salts, indicates that they lack a carbonyl group. Apparently the 1620–1630 cm^{-1} absorption band in the spectra of the salts is due to vibrations of the pyrrolene ring, with a double bond in the α-position. The presence in the spectra of dipyrrylmethenes (see e.g., [2]) of a characteristic strong band at ~ 1620 cm^{-1} is possibly also due to vibrations of the pyrrolene ring.

In the IR spectra of salts C=O and N–H absorption bands, and the presence of =NH$^+$ absorption as well as of associated hydroxyl, corresponds to structures II and III for salts of α-acetyl- and α-formylpyrroles.

The absorption band at about 1800 cm^{-1} in the case of salts of α-carbonylpyrroles is shifted in the direction of lower frequency compared with the β-compounds (see table and [1]). This factor (along with the presence or absence of a band at 1620–1630 cm^{-1}) can be used to ascertain the position of the acetyl or formyl group in the ring.

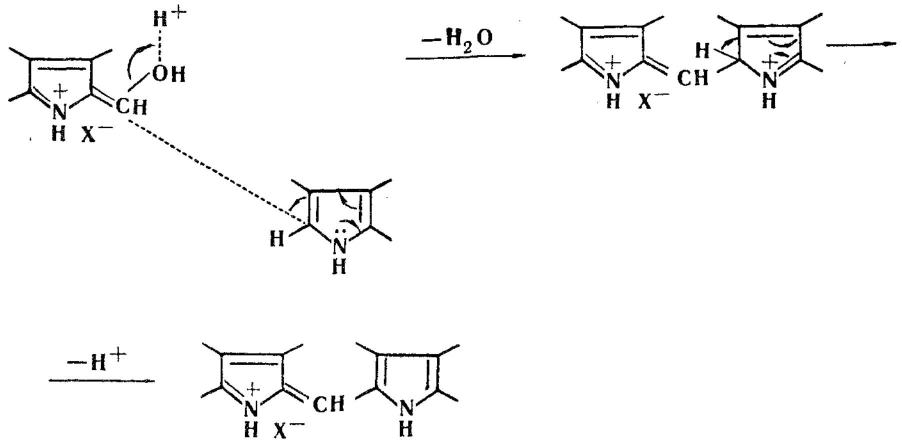
The genesis of structures I, II, and III in formation of salts of acetyl and formylpyrroles explains the reactivities of these compounds in acids. In the case of salts of 3-acetyl-(I) and 3-formylpyrroles, the α-position 5 is activated in respect of electrophilic substitution, while at the same time the α-position 2 is completely deactivated, and electrophilic attack hindered. In the case of salts of 2-acetyl- and 2-formylpyrroles (II and III), the β-position 4 must be activated because of polarization of the double bond in position 3, 4 under the action of the NH$^+$ group, but on account of the remoteness of the NH$^+$ group, this will be to a considerably less extent, than is the case for the α-position in 3-acetyl- and 3-formylpyrroles. In this case (II and III) the α-position 5 is deactivated. This can be illustrated by the following examples. In an attempt to prepare 2, 4-dimethyl-3-pyrrolealdehyde hydrochloride, Treibs and Kolm isolated only dipyrrylmethene [3]; there the reactivity of the α-position 5 is enhanced to such an extent that self-condensation of two molecules of hydrochloride takes place. In the case of the salt of 2, 4-dimethyl-5-pyrrolaldehyde, the reactivity of the β-position is insufficient, and dipyrrylmethene is not formed. We also did not observe formation of dipyrrylmethene when preparing the hydrochloride of 3-methyl-4-(β-carboxyethyl)-pyrrolaldehyde-2 (Table 4), though there the pyrrole ring has an unsubstituted α-position; however, in structure III, that α-position is completely deactivated.

Formation of dipyrrylmethenes from pyrrolaldehydes and pyrrole derivatives with an unsubstituted position proceeds under acid-catalysis, and obviously includes salt formation. Assumed mechanisms of formation of dipyrrylmethenes [4, 5] postulate formation of the dipyrrylcarbinol X as the first stage. Such carbinols were isolated when pyrrolaldehydes reacted with α-unsubstituted pyrroles in neutral solution, but with acid catalysis they split off water to give dipyrrylmethenes, and their occurrence in acid solution was not demonstrated. The mechanism, including the intermediate formation of dipyrryl carbinol, can be represented thus:



The carbonium ion VIII, formed by reaction of aldehyde VII with acid, attacks the unsubstituted position in compound IX, giving the dipyrrylcarbinol X, which splits off water, and is converted to the dipyrrylmethene XI. Such a mechanism draws an analogy between aldehydes of other classes (aliphatic, aromatic) and pyrrolaldehydes, i.e., it actually regards the formyl group as isolated from the pyrrole ring. The aldehyde salt, appearing as the carbonium ion VIII, must be regarded as a very reactive intermediate compound.

Further, in salt formation the aldehyde group does not react in isolation from the pyrrole ring, and the salt of structure III is a rather stable compound. So it seems probable that the dipyrrylmethene is formed from a salt of structure III and an α-unsubstituted pyrrole, with the dipyrrylcarbinol stage voided, the equations being:



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