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Abstract

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STRUCTURE OF SALTS OF 3-ACETYLPYRROLE DERIVATIVES AND THE MECHANISM OF FORMATION OF DIPYRRYLMETHANES

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The nitrogen atom of the pyrrole nucleus has relatively weak basicity because its lone pair is involved in the formation of the aromatic structure. Nevertheless, a number of pyrrole derivatives are capable of forming fairly stable salts with various acids ([1,2]).

Recently, hypotheses have been advanced to explain the enhanced reactivity of pyrrole derivatives in an acidic medium ([2–6]). Treibs and co-workers ([2,3,5]) assign pyrrolene structures I and II to pyrrole salts and explain pyrrole transformations by the reactivity of the methylene group. According to their proposal, if the α-pyrrolene structure I enters into a reaction, the reaction proceeds in the α-position; in the case of the β-pyrrolene structure II, in the β-position.

(I) (II) (III) (IV)

Bullock ([6]) showed the possibility of the existence of structure III for alkylpyrrole chlorohydrates in the crystalline state on the basis of their infrared spectra; at the same time, Abraham, Bullock, and Mitra ([7]), in considering the NMR spectra of alkylpyrroles in aqueous acid solutions, came to the conclusion that under these conditions structure I predominates.

As for acetylpyrroles, Treibs and Kolm ([2]) derive the structure of their salts from the limiting resonance structures of the bases and suggest that any one of these forms may be favorable in each particular case depending on other substituents, or else that the salt exists as a mixture of tautomeric forms. In order to explain the reactions of α-unsubstituted β'-acetylpyrroles (in particular the formylation reaction), these authors prefer structure IV.

The infrared spectra of 3-acetylpyrrole derivatives show a considerable displacement of the lone pair of the ring nitrogen toward the oxygen of the acetyl group; the absorption frequency of the C=O group (1633 cm^{-1} for 3-methyl-4-acetylpyrrole, 1624 cm^{-1} for 2,4-dimethyl-3-acetylpyrrole, 1622 cm^{-1} for 3,3′,5,5′-tetramethyl-4,4′-diacetyldipyrrylmethane) is strongly lowered in comparison with the frequency of the same group in aliphatic ketones ($\sim$ 1715 cm^{-1}) (all data are given for suspensions of crystals in vaseline oil; therefore an additional lowering of the frequency due to intermolecular hydrogen bonds must be taken into account). The displacement of electrons from the nitrogen atom toward the oxygen atom in compound V may lead to the appearance of a noticeable negative charge on the oxygen atom, and the molecule will react in the ionic form VI, giving a salt of structure VII.

$$(\mathrm{V}) \longrightarrow (\mathrm{VI}) \xrightarrow{\mathrm{HX}} (\mathrm{VII}) \quad (\mathrm{VIII})$$

Electron-acceptor substituents in the nucleus lower the electron density on the oxygen atom. This is clearly seen in the spectra of compounds containing such a strongly electronegative group as the β,β-dicyanovinyl group. In the infrared spectrum of 2,4-dimethyl-3-acetyl-5-(β,β-dicyanovinyl)pyrrole (m.p. 193–194°)

Found, %: C 67.43; H 4.87; N 19.86
$C_{12}H_{11}ON_3$. Calculated, %: C 67.59; H 5.20; N 19.70

obtained in 84% yield by condensation of equimolar amounts of 2,4-dimethyl-3-acetylpyrrole-5-aldehyde and malononitrile in the presence of catalytic amounts of diethylamine, the absorption band of the C=O group is at 1655 cm^{-1}. The simultaneous presence of dicyanovinyl and carbethoxy groups in 3-methyl-4-acetyl-2-carbethoxy-5-(β,β-dicyanovinyl)pyrrole ([8]) leads to an increase in the frequency of the C=O group to 1673 cm^{-1}. Electronegative groups, by lowering the electron density on the oxygen atom, hinder or make impossible the formation of salts.

The probability of structure VII for the salts of 3-acetylpyrrole derivatives is confirmed by data on salt formation in amides. Infrared ([9]) and NMR spectroscopy ([10]) data show that, upon formation of an amide salt, protonation occurs not at the nitrogen atom but at the oxygen atom, with formation of the iminohydrinic structure VIII.

Derivatives of 3-acetylpyrrole may be regarded as vinylogs of amides, in which the oxygen atom possesses an even higher electron density, as follows from the infrared spectra (the C=O absorption band at $\sim$ 1630 cm^{-1}, compared with $\sim$ 1650 cm^{-1} for secondary amides and 1688 cm^{-1} ([8]) for acetamide). Thus, the occurrence of structure VII, vinylogous to VIII, is even more probable.

Salts of pyrroles and dipyrrylmethanes were obtained by treating solutions of the bases in ether (IX, see Table 1) or acetone (X, XII, XIII) with an ethereal solution of dry hydrogen chloride, in yields of 80–90%. The hydrochloride of meso-substituted dipyrrylmethane XI was formed upon addition

Table 1

Physicochemical constants of the compounds

Compound	Hydrochloride: m.p., °C	Hydrochloride: IR spectrum, cm^{-1}, O–H	Hydrochloride: IR spectrum, cm^{-1}, N–H	Hydrochloride: IR spectrum, cm^{-1}, $>\overset{+}{N}-H$	Hydrochloride: IR spectrum, cm^{-1}, C–O	Hydrochloride: IR spectrum, cm^{-1}, C–N	Base: IR spectrum, cm^{-1}, N–H	Base: IR spectrum, cm^{-1}, C=O	Preparation
IX	121–122.5 (115–120(?))	3360–3040	–	1798, 1957, 2000–2370	–	1595, 1571	3230	1624	([12])
X	183–184	3500–3000		1825, 1974, 2600–2000	–	1572	3190	1622	([13])
XI	159–160	3500–3000	–	2100 1700	–	1592	3308	1622	([14])
XII	108–110	3500–3000	3350	1945 (weak)	1702 (carbethoxy)	1588	3354, 3262	1645, 1707 (carbethoxy)	([14])
XIII	203–204	3500–3000	3160	1965, 2300 (broad), 2500 (broad)	1658, 1708 (carbethoxy)	1587	3325, 3140	1642, 1612, 1716 (carbethoxy)	([14])

of a solution of hydrogen chloride in ether to a solution of 2,4-dimethyl-3-acetylpyrrole in acetone.

The salts obtained remain unchanged for a fairly long time when protected from moisture; however, on standing in air they slowly decompose. Treatment of alcoholic solutions of the salts with an aqueous solution of sodium bicarbonate gave the corresponding bases.

The infrared spectra of the salts provide strong evidence in favor of structure VII. In the spectrum of 2,4-dimethyl-3-acetylpyrrole hydrochloride (IX, see Table 1 and Fig. 1,a), the absorption bands of $C = O$ (1624 cm^{-1}) and $N - H$ (3230 cm^{-1}), present in the spectrum of the base, disappear completely. Instead, characteristic "immonium" bands appear at 1798 cm^{-1} and 1957 cm^{-1}

$$(C = \overset{+}{N} - H).$$

The broad absorption band at 2370–2000 cm^{-1} can also be assigned to absorp-

Fig. 1. IR spectra of derivatives of 3-acetylpyrrole in Vaseline oil: a –IX, b –X. Solid curves –base, dashed –hydrochloride.

Figure 1: Fig. 1. IR spectra of derivatives of 3-acetylpyrrole in Vaseline oil: a –IX, b –X. Solid curves –base, dashed –hydrochloride.

tion of the

$$C = \overset{+}{N} - H$$

group. The broad absorption in the region 3360–3040 cm^{-1} is due to the presence of polymeric association of the hydroxyl. The band at 1571 cm^{-1}, appearing in the hydrochloride and absent in the base, probably belongs to absorption of the $C = N$ group. These data make it possible to assign to 2,4-dimethyl-3-acetylpyrrole hydrochloride (IX, see Table 1) structure XV.

Fig. 1. IR spectra of derivatives of 3-acetylpyrrole in Vaseline oil: **a** –IX, **b** –X. Solid curves –base, dashed –hydrochloride.

Unstable 3-methyl-4-acetylpyrrole hydrochloride (m.p. 76–76.5°) partially loses hydrogen chloride even on drying in vacuum and therefore always contains an admixture of the base; its IR spectrum is similar to the spectrum of IX (broad absorption in the region 3500–3060 cm^{-1}, absorption bands of $C = \overset{+}{N} - H$ at 1820, 1970, and 2300–2000 cm^{-1}, $C = N$ at 1575 cm^{-1}), but owing to decomposition of the salt there is a weak absorption band of $C = O$ (1633 cm^{-1}, as in the pure base).

A similar picture is observed in the spectra of the hydrochlorides of dipyrrylmethanes (X–XII, see Table 1 and Fig. 1,b). In all these compounds, on salt formation the $C = O$ absorption band present in the spectrum of the base disappears. Dipyrrylmethane XIII, containing two acetyl groups, forms a monohydrochloride, since the basicity of one of the pyrrole nuclei is lowered owing to the presence of the carbethoxy group; therefore, in the spectrum of its salt there is an absorption band of the acetyl $C = O$, shifted, however, toward higher frequencies; the immonium band at 1965 cm^{-1} shows that salt formation apparently proceeds analogously. In the spectrum of salt XII the immonium band at 1945 cm^{-1} is weakly expressed, and in the spectrum of salt XI a clearly expressed absorption maximum is absent, although in the region 2100–1700 cm^{-1} broad absorption is observed with a small maximum at 1700 cm^{-1}; in the spectrum of the dihydrochloride of dipyrrylmethane X there are immonium bands analogous to the bands in the spectrum of IX. The broad absorption in the region 3500–3000 cm^{-1} for X–XIII indicates the presence of hydroxyl polyassociates. The $N - H$ absorption bands in the salts either disappear completely–in the case of formation of dihydrochlorides (X, XI)–or one band remains against the background of broad hydroxyl absorption–in the monohydrochlorides (XII, XIII).

reaction scheme: mechanisms (a) and (b) leading through intermediates (XIV), (XV), (XVI), (XVII), (XVIII), and (XIX)

Figure 2: reaction scheme: mechanisms (a) and (b) leading through intermediates (XIV), (XV), (XVI), (XVII), (XVIII), and (XIX)

These data make it possible, with a high degree of probability, to assign the following structures to the salts of dipyrrylmethanes: XVII –to compounds XII and XIII (see Table 1), XIX –to salts X and XI.

The presence of structure VII in 3-acetylpyrrole derivatives makes it possible to formulate probable mechanisms for the formation of unsymmetrical

and symmetrical acetyl-containing dipyrrolylmethanes in the following way.

In the case of formation of an unsymmetrical dipyrrolylmethane (a), the carbocation XIV, arising upon detachment of a halide or hydroxide anion from the corresponding pyrrole derivative, attacks the pyrrole salt XV, which is formed in the presence of acid. The attack occurs at the corresponding α-position, which has increased electron density as a result of strong polarization of the double bond under the action of the NH^+ group. The α-pyrrolenine derivative XVI formed eliminates a proton, giving the dipyrrolylmethane salt XVII, which, as a result of solvolysis, is converted into the free base XVIII. An analogous process takes place in the case of formation of symmetrical dipyrrolylmethanes (b).

Apparently, other electrophilic substitution reactions proceeding under acid catalysis (for example, formylation with hydrocyanic acid and hydrogen chloride) in 3-acetylpyrroles also proceed by a similar mechanism, since in an acidic medium salts of structure VII are first formed. Thus, the reactivity of the compounds of this series investigated is not explained by the presence of an active methylene group, as Treibs and co-workers postulated [2]. Moreover, structure VII is formally comparable with the β-pyrrolenine structure II; however, the α-position is the reactive one.

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