PROTONATION OF CARBETHOXYPYRROLES

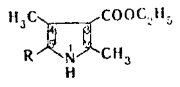
M. I. Struchkova, G. G. Dvoryantseva,
N. P. Kostyuchenko, Yu. N. Sheinker,
Yu. E. Sklyar, and R. P. Evstigneeva

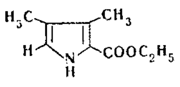
UDC 547.746:543.422.6:541.67

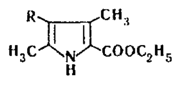
The PMR and UV spectra of the bases and conjugate acids of carbethoxy derivatives of pyrrole were investigated. The conjugate acids of 3-carbethoxypyrroles in 22-25 N H_2SO_4 have the α-pyrrolene structure, which corresponds to protonation of these compounds at the 5-C atom of the pyrrole ring. The protonation of 2-carbethoxypyrroles under the same conditions proceeds through the formation of an intermediate form, which is converted to the stable cation form in several hours. The stable form of the conjugate acid of 3,4-dimethyl-2-carbethoxypyrrole has the α-pyrrolene structure, which corresponds to the addition of a proton to the unsubstituted 5-C ring carbon atom. The structures of the stable forms of the conjugate acids of 2-carbethoxypyrroles that are substituted in the 5 position of the methyl group correspond to protonation of these compounds at the nitrogen atom of the pyrrole ring.

A study of the protonation of alkylpyrroles in mineral acid solutions [1-4] has demonstrated that the addition of a proton proceeds at the α- or β-carbon atom of the pyrrole ring. The presence of electron-acceptor substituents in the pyrrole ring leads to the possibility of the formation of other protonated forms [5-8], and the position of the protonation center of the molecule depends both on the properties of the substituent and on its position in the ring.

In order to study the protonation of carbethoxy derivatives of pyrroles, we measured the PMR and UV spectra of the bases and conjugate acids of I-VII. The experimental results are presented in Tables 1 and 2.

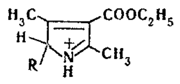

I-III


IV


V-VII

I, V R=H; II, VI R=CH_3; III, VII R=C_2H_5

From a comparison of the PMR spectra of the neutral and protonated forms of 3-carbethoxypyrroles I-III, which were measured, respectively, in $CDCl_3$ and 22-25 N H_2SO_4 (Fig. 1 and Table 1), it follows that the addition of a proton in these compounds proceeds at the 5-C ring carbon atom to form conjugate acids Ia-IIIa:


Ia-IIIa

The signal of the 5-H proton in the spectrum of base I is a quartet due to spin–spin coupling (SSC) with the protons of the 4-CH_3 group, the signal of which appears as a doublet with J = 1.2 Hz. The signal of the protons of the methyl group in the 2 position is observed as a singlet. The assignment of the signals

---

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. M. V. Lomonosov Moscow Institute of Precision Chemical Engineering. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 336-341, March, 1972. Original article submitted May 10, 1971.

TABLE 1. Chemical Shifts in the PMR Spectra of Bases and Conjugate Acids of Carbethoxypyrroles

Compound	Cpd. form.*	Chemical shifts, δ, ppm†				
		1	2	3	4	5
2,4-Dimethyl-3-carbethoxypyrrole (I)	B	8,34 b	2,45 s	1,33 t 4,26 q	2,21 d	6,32 q
	C	—	2,84 s	1,46 t 4,44 q	2,69 s	4,98 b
2,4,5-Trimethyl-3-carbethoxypyrrole (II)	B	8,07 b	2,44 s	1,33 t 4,24 q	2,15 s	2,10 s
	C	—	2,82 s	1,42 t 4,44 q	2,59 s	1,60 d 4,98 b
2,4-Dimethyl-5-ethyl-3-carbethoxypyrrole (III)	B	8,02 b	2,44 s	1,33 t 4,26 q	2,15 s	1,13 t 2,53 q
	C	—	2,83 s	1,45 t 4,46 q	2,63 s	0,93 t 1,46 q 4,92 b
3,4-Dimethyl-2-carbethoxypyrrole (IV)	B	8,75 b	1,34 t 4,29 q	2,25 s	1,98 s	6,64 d
	C	—	1,42 t 4,16 q	2,30 s	2,12 s	4,88 b
3,5-Dimethyl-2-carbethoxypyrrole (V)	B	8,81 b	1,33 t 4,29 q	2,23 s	5,76 d	2,28 s
	C	4,78 b	1,37 t 4,04 q	2,38 d	6,67 b	2,64 st
3,4,5-Trimethyl-2-carbethoxypyrrole (VI)	B	8,95 b	1,32 t 4,29 q	2,16 s	1,90 s	2,23 s
	C	4,67 b	1,37 t 4,07 q	2,24 s	2,00 s	2,58 t
3,5-Dimethyl-4-ethyl-2-carbethoxypyrrole (VII)	B	8,86 b	1,32 t 4,27 q	2,18 s	1,02 t 2,33 q	2,25 s
	C	4,65 b	1,37 t 4,09 q	2,27 s	1,09 t 2,47 q	2,60 t

---

*The following symbols were used: B is the base, and C is the conjugate acid.

†The symbols are as follows: s is singlet, d is doublet, t is triplet, q is quartet, b is broad signal, and st is split triplet.

TABLE 2. UV Spectra of Bases and Conjugate Acids of Carbethoxypyrroles

Compound	Cpd. form.*	Medium	λ_{max}, nm	ε
2,4-Dimethyl-3-carbethoxypyrrole (I)	B	H_2O	262 235,5	5080 8960
	C	15 N H_2SO_4	252	5230
2,4,5-Trimethyl-3-carbethoxypyrrole (II)	B	H_2O	275 236,5	3590 6300
	C	15 N H_2SO_4	255	4800
2,4-Dimethyl-5-ethyl-3-carbethoxypyrrole (III)	B	H_2O	272 227	4800 9200
	C	15 N H_2SO_4	253	5080
3,4-Dimethyl-2-carbethoxypyrrole (IV)	B	H_2O	275 250	15050 11000
	C**	28 N H_2SO_4	288	4800
	C	28 N H_2SO_4	277	5000
3,5-Dimethyl-2-carbethoxypyrrole (V)	B	H_2O	279 245	15800 3000
	C**	22 N H_2SO_4	263 220	4570 4300
	C	22 N H_2SO_4	253	4800
3,4,5-Trimethyl-2-carbethoxypyrrole (VI)	B	H_2O	287 250	16650 4000
	C**	17,3 N H_2SO_4	273	5370
	C	17,3 N H_2SO_4	263	5400
3,5-Dimethyl-4-ethyl-2-carbethoxypyrrole (VII)	B	H_2O	285 247	19350 6000
	C**	17,3 N H_2SO_4	275	5620
	C	17,3 N H_2SO_4	263	5600

---

*The following symbols were used: B is the base, C is the conjugate acid, and C** is the unstable form of the conjugate acid.

of the protons of the CH_3 groups follows from a comparison of the spectra of I-III and is in agreement with the data in [9]. The signal of a methylidyne proton is absent in the spectrum of conjugate acid Ia, and a broad signal with an intensity of two proton units, which should be ascribed to the methylene protons attached to the sp^3-hybridized 5-C atom, appears at stronger field ($\delta = 4.98$ ppm). On passing from base I to conjugate acid Ia, the signals of the 2- and 4-CH_3 groups are shifted to weak field by 0.4-0.5 ppm. One should note the broadening of the signal of the 2-CH_3 group in the spectrum of Ia, which is apparently due to long-range SSC with the methylene group attached to 5-C.

The signals of the methyl protons in the spectrum of base II are singlets, and the signal of the 2-CH_3 group is situated at weak field. A broad multiplet of the methylene proton ($\delta = 4.98$ ppm) and a doublet of the 5-CH_3 methyl group ($\delta = 1.60$ ppm, $J = 7.0$ Hz) are observed in the spectrum of conjugate acid IIa. The

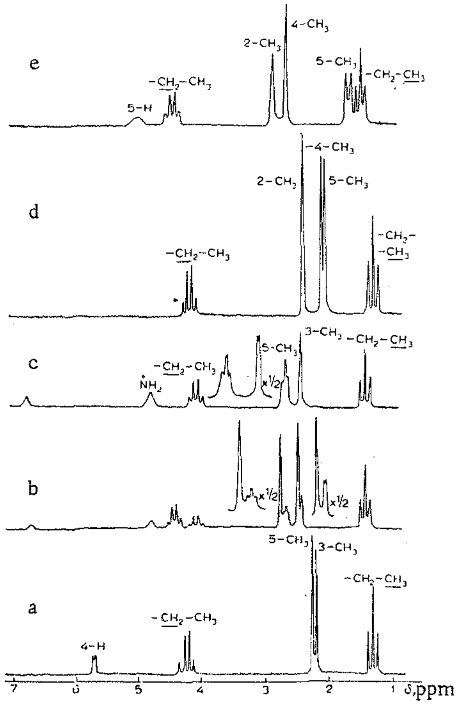


Fig. 1

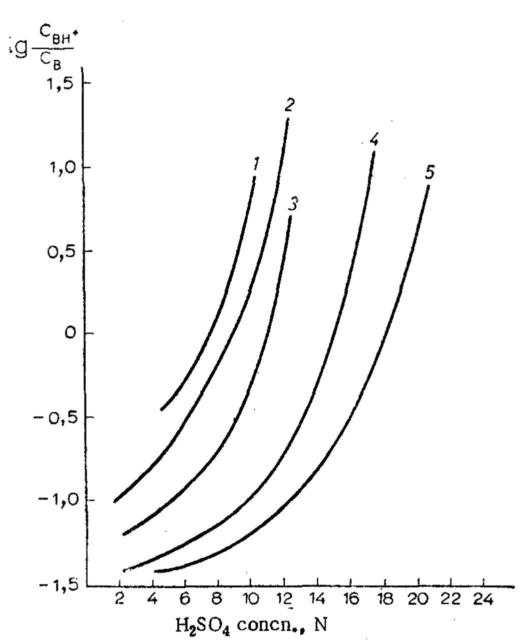


Fig. 2

Fig. 1. PMR spectra of the base (a), mixture of the intermediate and stable forms of the conjugate acid (b), and of the stable form of the conjugate acid (c) of 3,5-dimethyl-2-carbethoxypyrrole (V); of the base (d) and conjugate acid (e) of 2,4,5-trimethyl-3-carbethoxypyrrole (II).

Fig. 2. Indicator curves of carbethoxypyrroles I (1), II (2), VI (3), V (4), and IV (5).

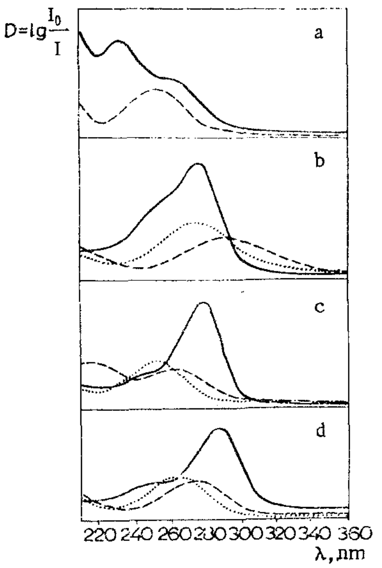


Fig. 3. UV spectra of bases (——) and conjugate acids [---- (intermediate form), ... (stable form)] of carbethoxypyrroles II (a), IV (b), V (c), and VI (d).

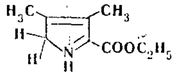
signals of the methyl groups in the 2 and 4 positions are shifted to weak field, just as in Ia, and broadening of the 2-CH_3 signal is observed. The changes in the PMR spectrum on passing from the base to the conjugate acid of III are similar in character and also correspond to addition of a proton to the α-5-C carbon atom.

The protonation of 3-carbethoxypyrroles I-III leads to characteristic changes in the UV spectra at 210-360 nm. Two bands with absorption maxima at 260-275 nm (ε 3600-5500) and 225-240 nm (ε 6000-10,000) are observed in this region in the spectra of the bases. Both bands should be ascribed to $\pi \rightarrow \pi^*$ transitions [10]. Protonation at the α-carbon atom of the pyrrole ring leads to a hypsochromic shift of these transitions, and only one absorption band at 250-255 nm (ε 4800-5300) is observed in the investigated region in the spectra of conjugate acids Ia-IIIa. Similar changes in the UV spectra on passing from the bases to the conjugate acids, which have the α-pyrrolene structure, have been observed for alkylpyrroles [1]. It should be noted that both the UV and PMR spectra of 3-carbethoxypyrroles in 22-25 N H_2SO_4 do not change with time, which characterizes the α-pyrrolene structure Ia-IIIa as the stable form of the cations of these compounds.

A change in the position of the carbethoxy group relative to the nitrogen atom of the pyrrole ring has a considerable effect on the proton-acceptor capacity of the compounds of the type under investigation. Thus it follows from a comparison of the indicator curves (Fig. 2) that the basicity decreases appreciably on passing from β-

carbethoxypyrroles I and II to the corresponding α-isomers IV and VI. A study of the PMR and UV spectra of α-carbethoxypyrroles IV-VII demonstrated that protonation of these compounds in 22-25 N H_2SO_4 proceeds through the generation of an intermediate form, which is converted to the stable form of the conjugate acid in several hours. All of the signals that pertain to the intermediate forms of cations of IV-VII (Fig. 1) in the PMR spectra are shifted to weak field relative to the corresponding signals of the stable forms. Moreover, the greatest difference between the chemical shifts in the intermediate and stable forms of the cations is observed for the methylene protons of the carbethoxy group (~0.3 ppm). The signals of the protons of the methyl groups of the intermediate forms of the cations of all of the examined 2-carbethoxypyrroles are singlets, and their positions in the spectrum do not correspond to a change in the hybridization of the pyrrole ring carbon atom bonded to them. All of these data indicate that the structures of the intermediate forms possibly correspond to addition of a proton to the carbonyl atom of the oxygen of the carbethoxy group, but the proof of such structures requires additional investigation.

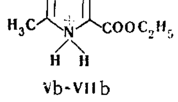
The α-pyrrolene structure (IVa) corresponds to the stable form of the conjugate acid of 3,4-dimethyl-2-carbethoxypyrrole. The changes in the PMR spectrum on passing from base IV to conjugate acid IVa are similar to those described for I. The signal of a methylidyne proton in the 5 position, which is observed in the spectrum of the base as a doublet (J = 3.0 Hz) at 6.64 ppm, is absent in the spectrum of IVa, and a broad signal of a methylene group with an intensity of two proton units appears at 4.88 ppm. The singlets of the 3- and 4-CH_3 groups are shifted to weak field relative to the spectrum of base IV.



IVa

The structure of the stable forms of the conjugate acids of 2-carbethoxypyrroles V-VII, which are substituted with a methyl group in the 5 position, does not correspond to protonation of these compounds at the pyrrole ring carbon atom. This conclusion follows primarily from the shift in the signals of the protons of the methyl groups to weak field and from the absence of a vicinal J_{CH_3H} SSC constant (~7 Hz). A signal of a 4-H methylidyne proton (δ = 6.67 ppm), which is shifted to weak field by 0.91 ppm relative to the corresponding signal in the spectrum of the base, is observed in the spectrum of the conjugate acid of 3,5-dimethyl-2-carbethoxypyrrole (V). The broad signal with an intensity of two proton units that is observed in the spectra of the stable forms of the conjugate acids of V-VII at 4.6-4.8 ppm can be assigned to the protons of the $\overset{+}{N}H_2$ group. This assignment is confirmed by the character of the splitting of the signal of the proton of the methyl group in the 5 position, which appears in these spectra as a triplet with an SSC constant of 3.0 Hz. The double-resonance method established that this splitting is due to SSC with the protons, the signal of which is observed at 4.6-4.8 ppm. The triplet of the 5-CH_3 group in V is additionally subsplit due to SSC with the proton in the 4 position ($J_{4\text{-}H,\ 5\text{-}CH_3} = 1.2$ Hz). The signal of the protons of the 3-CH_3 methyl group (doublet at 2.38 ppm) is split with approximately the same constant. The signals of the $\overset{+}{N}H_2$ group and the 4-H proton are absent in the spectrum of the cation of V in 22 N D_2SO_4, and splitting of the signals of the methyl groups is not observed, which indicates the comparatively high rate of exchange of the methylidyne protons of the pyrrole ring by deuterium in the conjugate acids of 2-carbethoxypyrroles. The absence of signals of methylidyne protons in the spectra of the intermediate forms of the cations of α- and β-unsubstituted IV and V is probably associated with this.

Thus it follows from an examination of the PMR spectra that the structures of the stable (in 22-25 N H_2SO_4) forms of the conjugate acids of V-VII correspond to the addition of a proton to the nitrogen atom of the pyrrole ring (structures Vb-VIIb).



Vb-VIIb

Peculiarities in the protonation of α-carbethoxypyrroles also appear in the UV spectra of these compounds. The spectra of aqueous solutions of bases IV-VII at 210-360 nm are characterized by the presence of two bands with absorption maxima at 275-285 nm (ε 15,000-19,000) and 240-250 nm (ε 4000-11,000). A less intense short-wave band is observed as a shoulder on the high-energy wing of the long-wave band (Fig. 3). Like the PMR spectra, the UV spectra of the cations of these compounds change with time. Thus on passing from the 3,4-dimethyl-2-carbethoxypyrrole base (IV) to the corresponding cation, one observes a bathochromic shift of the absorption bands and a considerable decrease in the intensity of the long-wave band. A broad band with an absorption maximum at 228 nm (ε 4800) is present in the spectrum of the conjugate acid measured directly after preparation of the solution. This band is asymmetrical in form, and an inflection point at 310-320 nm can be isolated on the low-energy wing of the band. This sort of band structure is possibly due to the fact that the less intense, low-energy transition is masked by a more intense band with λ_{max} 288 nm. Measurement of the spectrum as a function of time demonstrated that the transition to the stable form of the conjugate acid is accompanied by a shift in this band to the short-wave region. A symmetrical band with an absorption maximum at 277 nm (ε 5000) is observed in the spectrum of the stable form of conjugate acid IVa.

A considerable decrease in the intensity and a shift of the absorption band maxima to the short-wave region by 10-20 nm occurs on passing from the neutral to the protonated forms of V-VII. The transition to the stable forms of the conjugate acids of these compounds causes a further hypsochromic shift of the bands by ~10 nm without an appreciable change in their intensities.

EXPERIMENTAL

Carbethoxypyrroles I [11], II, III [12], IV [13], V, and VI [14] were obtained via known methods; VII was obtained in analogy with VI, and the melting point was in agreement with the literature value [15]. The stability of the investigated compounds with respect to acid was demonstrated by dissolving them in 36 N H_2SO_4 and isolating the starting bases by the addition of water after 2 h. The identical character of the compounds isolated in this way and the starting bases was demonstrated from a comparison of their IR spectra, from mixed melting-point determinations, and from the R_f values obtained from thin-layer chromatography.

The PMR spectra of 2% solutions of the compounds in $CDCl_3$ and in 22-25 N H_2SO_4 were measured with a JNM-4H-100 spectrometer. The chemical shifts are presented on the δ scale. Tetramethylsilane (for solutions in $CDCl_3$) and sodium 4,4-dimethyl-4-silapentane-1-sulfonate (for solutions in H_2SO_4) were used as the internal standards.

The UV spectra were measured with a Hitachi EPS-3T spectrophotometer. Weighed samples of the investigated substances were dissolved in 96% ethanol, and the solutions were then further diluted with titrated solutions of sulfuric acid. The concentration of the 2-carbethoxypyrroles in the solutions was $4 \cdot 10^{-5}$ M, while the concentration of the 3-carbethoxypyrroles was $6 \cdot 10^{-5}$ M. The ethanol concentration in the measured solutions was 1%.

LITERATURE CITED

1. J. Chiang and E. B. Whipple, J. Am. Chem. Soc., 85, 2763 (1963).
2. E. B. Whipple, J. Chiang, and R. L. Hinman, J. Am. Chem. Soc., 85, 26 (1963).
3. R. J. Abraham, E. Bullock, and S. S. Mitra, Can. J. Chem., 37, 1859 (1959).
4. E. Bullock, Can. J. Chem., 36, 1686 (1958).
5. Yu. E. Sklyar, R. P. Evstigneeva, O. D. Saralidze, and N. A. Preobrazhenskii, Dokl. Akad. Nauk SSSR, 157, 367 (1964).
6. Yu. E. Sklyar, R. P. Evstigneeva, and N. A. Preobrazhenskii, Khim. Geterotsikl. Soedin., 216 (1966).
7. Yu. E. Sklyar, R. P. Evstigneeva, and N. A. Preobrazhenskii, Zh. Obshch. Khim., 40, 1877 (1970).
8. T. A. Melent'eva, T. F. Filippova, L. V. Kazanskaya, I. M. Kustanovich, and B. M. Berezovskii, Zh. Obshch. Khim., 41, 179 (1971).
9. M. W. Roomi and H. Dugas, Can. J. Chem., 48, 2303 (1970).
10. F. Momicchoilly and G. Del Re, J. Chem. Soc., B, 674 (1969).
11. H. Fischer and B. Walach, Ber., 58, 2820 (1925).
12. Yu. E. Sklyar, R. P. Evstigneeva, and N. A. Preobrazhenskii, Khim. Geterotsikl. Soedin., 70 (1969).
13. G. M. Badger, R. A. Jones, and R. L. Laslett, Austral. J. Chem., 17, 1157 (1964).
14. G. G. Kleinspehn, J. Am. Chem. Soc., 77, 1546 (1955).
15. H. Fischer and B. Walach, Ann., 450, 125 (1926).