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CARBONYL DERIVATIVES OF HETEROCYCLIC COMPOUNDS—II*

CARBOXYL DERIVATIVES OF PYRROLE

M. K. A. KHAN and K. J. MORGAN†
Department of Chemistry, The University, Birmingham

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Abstract—The IR spectra and rates of hydrolysis of the esters of pyrrole-1-, -2-, and -3-carboxylic acids and the pK_a values of the acids have been measured. The carbonyl stretching frequencies show that considerable mesomeric interaction occurs between the carboxyl group and the ring. The anomalously high ionization constant of the -2-acid and the high rate of hydrolysis of the -2-ester are ascribed to intramolecular hydrogen bonding in the anion and intermediate anion (IV) respectively.

THE chemical characteristics of the carboxyl group are well defined and those factors tending to modify both the structural properties and the chemical reactivity of the carboxyl group have been widely investigated. For both aromatic and aliphatic carboxyl derivatives it has been possible to correlate changes in structure and reactivity. In the aromatic series, where it is possible to alter the electrical characteristics of the aryl group without significantly modifying its steric requirements, precise correlations have been established in terms of the electrical properties of the aromatic system. Few attempts have been made to extend this approach to heteroaromatic systems.

The pyrrole carboxylic acids represent systems in which the spatial environment of the carboxyl group is not dissimilar from that of benzoic acid. Consequently the efficiency with which the electrical effects of the heterocyclic system are relayed to the carboxyl group—which is largely determined by steric factors—can be expected to be similar to that of benzoic acid. In an attempt to examine quantitatively the results of such interaction the dissociation constants of pyrrole-2- and -3- carboxylic acids and the IR spectra and rates of alkaline hydrolysis of the corresponding methyl esters and of ethyl pyrrole-1- carboxylate have been determined.

EXPERIMENTAL

Pyrrole-2-carboxylic acid.[1,2] Pyrrolyl magnesium iodide (from pyrrole, 20 g; Mg, 8 g and MeI, 47 g) was treated with ethyl chloroformate (7·5 g). A solution of the crude product in EtOH (80 ml) was boiled with KOH (21 g) for 3 hr and the free acid (7·5 g, 23%) m.p. 208°, was obtained by acidification.

The methyl ester, m.p. 73–74°, was prepared by the action of diazomethane on the acid.

Pyrrole-3-carboxylic caid. The acid was prepared from 1,3-di-(ethoxycarbonyl)-pyrrolid-4-one[3]

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† Present address: Department of Chemistry, University of Lancaster.

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by the method of Rapoport and Willson.[4] Extraction of the crude product from the aqueous phase with ether (5 × 200 ml) and then continuously with ether gave pyrrole-3-carboxylic acid (60%), m.p. 150–150·5°, more satisfactorily than by the use[4] of $CHCl_3$.

Methyl pyrrole-3-carboxylate, m.p. 87–88° was prepared by the action of diazomethane on the acid.

Samples of these acids and esters used for pK_a, hydrolysis, and IR measurements were recrystallized to constant m.p. before use.

*Ethyl pyrrole-*1*-carboxylate.*[5] Potassium pyrrole (from pyrrole, 20 g and K, 11 g) was treated with ethyl chloroformate (21 g) in dry ether. After 2 hr the solution was filtered and evaporated giving ethyl pyrrole-1-carboxylate (7·4 g) b.p. 75°/13 mm.

Alkaline hydrolysis of alkyl pyrrole carboxylates. Aqueous acetone (56%) was obtained by diluting water (400 ml) to 1 l. with acetone which had previously been dried (K_2CO_3) and distilled through an efficient column.[6] Solutions (0·1 N) of NaOH and ester in aqueous acetone were equilibrated separately at the reaction temp and at the start of the reaction equal vols (50 ml) were mixed. At suitable intervals aliquots (10 ml) were withdrawn, added to an excess of standard HCl and then back-titrated using cresol red as indicator. Rate constants were calculated from the expression $k = 1/t(x/a(a - x))$.

Ionization constants of pyrrole carboxylic acids. A solution of acid (0·01 M) in water free of CO_2 was equilibrated at 20°. A solution of KOH (0·1 N) free of carbonate, was added in 10 equal portions, each 0·1 equiv. During the addition the solution was stirred by a slow stream of O_2-free N_2. The pH was read after each addition using a Pye Ingold combined electrode type 405 and a Pye Dynacap pH meter. The electrode was standardized with borate and phthalate buffers both before and after the titration; no adjustment was required after the titration. The ionization constant was calculated in the usual way.[7] Using this method benzoic acid gave pK_a 4·12 (±0·01).

Infra-red spectra. Spectra were measured on a Perkin–Elmer Model 125 spectrometer using as appropriate cells of nominal thickness 10, 1 and 0·1 mm. Solvents were of spectroscopic grade or were purified by conventional methods. Frequencies in the carbonyl region were calibrated against H_2O and are probably accurate to ±1 cm^{-1}; in the N—H region, the accuracy is probably ±2 cm^{-1}.

RESULTS

Ionization constants. Values for the ionization constants of pyrrole-2- and -3-carboxylic acids determined potentiometrically were (as pK_a values) 4·39 ± 0·01 and 5·00 ± 0·01 at 20° respectively. A value of p$K_a{}^T$ of 4·45 at 30° for pyrrole-2-carboxylic acid has been obtained by Lumme[8] also using a potentiometric method; application of the usual activity correction[7] to the result reported here gives a resultant p$K_a{}^T$ of 4·43 at 20° in satisfactory agreement with this. Using a less well-defined method Scrocco and Nicolaus[9] have reported a value of pK_a 4·40. The value obtained for pyrrole-3-carboxylic acid is close to values reported previously from less precise determinations (4·95[9], 5·07[4]).

Rates of hydrolysis. The alkaline hydrolysis of methyl pyrrole-2- and -3-carboxylates and of ethyl pyrrole-1-carboxylate using sodium hydroxide in aqueous acetone was studied under second order conditions. The results are shown in Table 1; in all cases the results gave excellent second order plots.

The experimental procedure was checked by following the hydrolysis of methyl benzoate at 25° when the observed rate constant $9{\cdot}0 \times 10^{-3}$ l. mol^{-1}sec^{-1}, was in satisfactory agreement with that reported by Timms and Hinshelwood.[10] Rate constants for the hydrolysis of methyl pyrrole-2-carboxylate were obtained at 25, 35

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[7] A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases.* Methuen, London (1962).

[8] P. Lumme, *Suoman Kemistilehti* **33B**, 87 (1960).

[9] M. Scrocco and R. Nicolaus, *Atti Acad. Naz. Lincei, Rend.* **22**, 311 (1957).

[10] E. W. Timm and C. N. Hinshelwood, *J. Chem. Soc.* 862 (1938).

and 50°. The reaction of the -3-carboxylate was markedly slower and reliable results were obtained at 35 and 50° only. Using an Arrhenius extrapolation, the rate constant at 25° was estimated to be 0·059 × 10^{-3} l. $mol^{-1}sec^{-1}$.

The hydrolysis of methyl pyrrole-1-carboxylate is a fast reaction under the conditions used for the other esters. To enable a more satisfactory study of the kinetics to be made, the rate of hydrolysis of the corresponding ethyl ester was examined. Even so, this reaction is notably faster than those of the other esters and no attempt was made to obtain values at temperatures other than 25°. The values of the rate constants (k_2) for the hydrolyses under similar conditions of the methyl and ethyl esters of substituted benzoic acids[6,10,11] allow a value for the rate constant of methyl pyrrole-1-carboxylate to be derived. A plot of log k_2 (methyl ester) *vs* log k_2 (ethyl ester) forms a good straight line of the form log k_2 (ethyl ester) = 1·06 log k_2 (methyl ester) −0·4 for the benzoates. Provided that the entropy of reaction of ethyl pyrrole-1-carboxylate is not markedly different from that of the ethyl benzoates this leads to an estimated value of k_2 for methyl pyrrole-1-carboxylate of 68·3 × 10^{-3} l. $mol^{-1}sec^{-1}$ at 25°.

TABLE 1. RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF PYRROLE ESTERS USING SODIUM HYDROXIDE

	k_2(l. $mole^{-1}sec^{-1}$)		
Temperature	Methyl pyrrole-2-carboxylate.	Methyl pyrrole-3-carboxylate.	Ethyl pyrrole-1-carboxylate.
25·3	0·41 × 10^{-3}	(0·059 × 10^{-3})*	23·10 × 10^{-3}
35·5	0·995 × 10^{-3}	0·157 × 10^{-3}	—
49·7	3·39 × 10^{-3}	0·56 × 10^{-3}	—

* obtained by extrapolation.

Infra-red spectra. Spectra were measured for solutions of the pyrrole esters in a wide variety of solvents; the frequencies of bands in the N—H stretching region and in the carbonyl stretching region are given in Table 2. Values for the N—H stretching

TABLE 2. BANDS IN THE INFRA-RED SPECTRA OF PYRROLE CARBOXYLIC ESTERS

	N—H stretching bands (cm^{-1})			Bands in the carbonyl stretching region (cm^{-1})				
Solvent	Methyl pyrrole-2-carboxylate.		Methyl pyrrole-3-carboxylate.	Methyl pyrrole-2-carboxylate.		Methyl pyrrole-3-carboxylate.		Methyl pyrrole-1-carboxylate.
Hexane	3471	3320	3493	1704	1719	1716	1735	1758
Carbon tetrachloride	3465	3318	3483	1700	1716	1711	1732	1753
Acetonitrile	3350		3365	1703	1720	1708	1730	1749
Dioxan	3270		3305	1702	1720	1708	1731	1749
Nitromethane	3420		3436	1702	1721	1704	1731	1748
Methylene chloride	3452		3461	1698	1720	1704	1729	1746
Chloroform	3462		3473	1697	1721	1702	1731	1743
Dimethyl sulphoxide	3155		3170	1698	(1720)	1701	(1728)	1745
Bromoform	3455		3456	1692	1719	1700	1728	1742

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[11] C. K. Ingold and W. S. Nathan, *J. Chem. Soc.* 222 (1936).

frequencies of methyl pyrrole-2- and -3-carboxylates have been reported for carbon tetrachloride solutions by Scrocco *et al.*[12] Their spectra were obtained under conditions permitting a considerable degree of intermolecular hydrogen bonding so that in addition to bands at 3472 and 3490 cm^{-1} respectively the spectra of both esters showed bands due to associated N—H groups at ca. 3320 cm^{-1}. Recently Jones and Moritz[13] have reported that using dilute solutions of pyrroles two N—H bands arising from monomeric molecules can be detected. For ethyl pyrrole-2-carboxylate in carbon tetrachloride thay observed bands at 3483 and 3465 cm^{-1} and for methyl pyrrole-3-carboxylate at 3472 and 3457 cm^{-1}. Using 0·002 molar carbon tetrachloride solutions and with a spectral slit width of 2·5 cm^{-1}, it was not found possible to resolve such bands in our spectra although weak bands were indicated as points of inflexion at 3480 and 3468 cm^{-1} for methyl -2- and -3-carboxylates respectively. The two bands in the spectrum of the ester of pyrrole-2-carboxylic acid were ascribed by Jones and Moritz[13] to intramolecular bonding: *viz* N—H . . . O—C— and N—H . . . O(Et)—C—. The very small difference in frequency of the two bands implies that the bond energy of both forms is similar and their position suggests that any bonding must be weak. This is confirmed by the effects of solvent on the frequency of the N—H stretching band which does not show the characteristic behaviour of an intramolecular hydrogen bonded system.[14] Thus plots of ν_{N-H}(ester) *vs* ν_{N-H}(pyrrole) form good straight lines including the points for hexane and carbon tetrachloride solutions which in the presence of a significant amount of hydrogen bonding would have been expected to fall off the line.

The carbonyl region of the spectra of methyl pyrrole-2- and -3-carboxylates are complex. The spectra of concentrated solutions (2×10^{-2} molar) in hexane and carbon tetrachloride contain three bands near 1700 cm^{-1}; on dilution and in more polar solvents two bands remain. Clearly the concentration dependant band found in the non-polar solvents can be ascribed to associated molecules: under the same conditions the spectrum contains a band near 3200 cm^{-1} due to the correspondingly associated N—H group. This concentration dependant band has been reported previously[12] but erroneously attributed to intramolecular hydrogen bonding.

Of the two residual bands in both cases that at the higher frequency is largely unaffected in position—though not in intensity—by solvent, while the lower frequency band is markedly solvent dependent. The displacement of the lower frequency band by solvents parallels that of the carbonyl band of acetophenone and plots of ν (ester) *vs* ν_{CO}(acetophenone) give good straight lines. Clearly this band can be attributed to an unassociated carbonyl group. It is noteworthy that the points corresponding to hexane and carbon tetrachloride solutions of the -2-carboxylate lie off the line defined by the other solvents. While these deviations can be partly ascribed to the distortion of the band shape due to incomplete resolution of the lower and higher frequency bands, they may also indicate the existence of rotational isomerism in these solvents. The consequently changed environment of the ether and carbonyl oxygen atoms of the ester resulting in changed direct field interactions with the ring nitrogen atom would be reflected in differing carbonyl frequencies for the two isomers.

[12] M. Scrocco, L. Caglioto and V. Caglioto, *Atti Acad. Naz. Lincei, Rend.* **24**, 316 (1958).

[13] R. A. Jones and A. G. Mortiz, *Spectrochim. Acta* **21**, 295 (1965).

[14] L. J. Bellamy and H. E. Hallam, *Trans. Farad. Soc.* **55**, 220 (1959); A. J. Collings and K. J. Morgan, *J. Chem. Soc.* 3437 (1963).

Relatively weak interactions such as are to be expected in the pyrrole ester could give rise to the small deviations apparent from the solvent plot; larger effects are encountered in analogous furan and thiophen compounds accompanying the greater direct field interactions in these compounds.[15]

The position of the higher frequency band and the failure to detect in the N—H stretching region any significant amount of intramolecular hydrogen bonding make it unlikely that this band can arise from an intramolecularly bonded carbonyl group. That it could be due to the carbonyl frequency of a geometrical isomer of the form producing the lower frequency band is similarly unlikely particularly for the -3-carboxylate and would not account for the band's solvent insensitivity. As the solvent polarity increases and consequently the separation of the two bands in the carbonyl region increases, the relative intensity of the higher frequency band decreases. This behaviour suggests that the band has its origin in an overtone or combination band borrowing intensity by Fermi resonance with the carbonyl band.[16]

The spectra of ethyl pyrrole-1-carboxylate contain only one band in the carbonyl region (Table 2). The frequency of this band shows a dependence on solvent similar to that of acetophenone and it can be ascribed to the ester carbonyl stretching frequency.

DISCUSSION

In the absence of specific steric effects the influence of structural perturbations on side-chain reactivity of benzene derivatives can be quantitatively correlated with the electrical properties of the benzene ring. The most familiar expression of this is the Hammett equation:

$$\log k/k_0 = \rho\sigma$$

which has been found to apply to a wide range of side chain reactions in aromatic systems. In this expression it is customary to regard the substituent constant (σ) as a measure of the electrical perturbation of the parent phenyl compound resulting from the replacement of hydrogen, the reference group, by a substituent X. It is equally permissible[17] to consider the aromatic system as a unit and to use as reference the phenyl group. In this way the substituent constant provides a measure of replacing C_6H_5 by XC_6H_4. Apart from the formal designation of the substituent the practical differences arising from these approaches in benzenoid systems are small. However, an important consequence of the second approach is its ability to be extended to non-benzenoid systems, provided that their steric and direct field interactions do not differ significantly from those of the phenyl group. This extension of the Hammett treatment to naphthalene and other polycyclic aromatic systems has been successful[18] and it is possible to consider heterocyclic systems in the same way.*

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* While it is possible to regard 2-naphthoic acid as a 3,4-C_4H_4-disubstituted benzoic acid and isonicotinic acid as a 4-aza-benzoic acid, assigning σ-values to 3,4-C_4H_4, and 4—N=, this is conceptually unattractive since the structural perturbations leave the phenyl group largely unrecognizable. It is difficult to see how this treatment could be extented to the pyrrole ring.

[15] M. K. A. Khan and K. J. Morgan, unpublished results.

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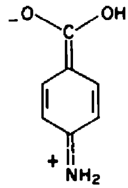

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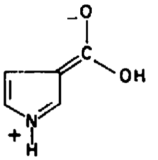

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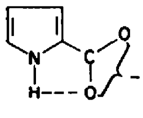

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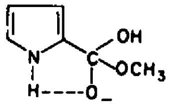

IV

To define the magnitude of the substitution constants it is necessary to assign an arbitrary value to the reaction constant for one process. The ionization of benzoic acids provides the accepted standard[19] and the reaction constant (ρ) for this process is defined as unity. By interpolating the ionization constants for pyrrole-2- and -3-carboxylic acids it is possible to obtain apparent sigma values for 2- and 3-pyrrolyl of −0·15 and −0·75 respectively.

The value of sigma provides a measure of the electron release from the aromatic system to the reaction centre. In those cases where the Hammett relationship applies accurately (i.e. side chain reactions) the changes in electron demand of the functional group between the initial and transition states in a rate process or between the two equilibrating states in a thermodynamic process do not markedly affect the extent of its interaction with the aryl system. Accordingly the Hammett sigma values can be regarded as a useful measure of the electron distribution in the ground state of the reacting molecule. In this way the apparent sigma constants for the pyrrolyl systems show that both positions have a higher electron density than is found in the phenyl group. This is in accord with expectation for in order that the pyrrole ring shall represent an aromatic system a pair of electrons from the nitrogen atom must be delocalized over the ring. It is also in agreement with dipole moment measurements which show that the nitrogen atom lies at the positive end of the electric dipole.[20]

The results of some semi-empirical molecular orbital calculations[21] have suggested that the 3-position in the pyrrole ring carries a higher electron density in the ground state than does the 2-position but more accurate calculations[22] indicate that the higher electron density is at the 2-position. The apparent sigma values might appear to resolve this issue in favour of a higher density at the 3-position were not any quantitative extension of the argument based on sigma values to be regarded as fallacious. The possibility of direct conjugation between a *p*-anilino group and a

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carboxyl group has been shown to result in a considerable distortion of the observed sigma value[23] since contributions of the form (I) will stabilize the carboxylic acid more than the anion by a mechanism not available to other systems. Similar interaction is possible in the pyrrole carboxylic acids where the introduction of a carboxyl group will grossly perturb the electron distribution of the pyrrole ring. Evidence for this is provided by the low carbonyl frequencies of the 2- and 3-pyrrole esters (*cf* methyl benzoate ν_{CO} 1735 cm^{-1} in hexane) which must be ascribed to contributing polar structures (e.g. II): the close relationship of the esters to the free acids implies that similar polar canonical forms play a significant part in their structures also.

The carbonyl frequencies of a series of methyl benzoates[24] have been found to correlate closely with the σ^+ constants developed by Brown.[25] These substituent constants are designed to accommodate the effects of the direct interaction of groups such as occurs in the transition state of the solvolysis of cumyl chlorides or the electrophilic substitution of aromatic compounds and for such processes replace the Hammett sigma constants. Interactions such as those indicated by the polar canonical structures written for the pyrrole esters (e.g. II) should be included by this treatment. The apparent σ^+ constants for 2-, and 3-pyrrolyl obtained by interpolation and extrapolation of the plot of ν_{CO} *vs* σ^+ are $-2{\cdot}0$, and $-1{\cdot}5$ respectively. It is clear from the nature of the extrapolation that these values are not quantitatively accurate but they are in agreement with the known susceptibility of the pyrrole ring to electrophiles and to the relative ease of attack at the 2-position. (A fuller discussion of this method of assessing reactivity parameters will be presented in a subsequent paper in this series.)

The readier polarizibility of the pyrrole ring towards the 2-position indicated by the IR measurements presents an apparent anomaly. Polarization in the acids similar to that found in the esters should leave the 2-carboxylic acid weaker than the 3-carboxylic acid. The failure to observe this implies either that the argument is fallacious or that an additional factor is modifying the relative acidity of the 2- and 3-carboxylic acids. While there appear to be no abnormal structural features associated with the 3-carboxylic acid, the proximity of the imino function to the carboxyl group in the 2- acid can provide such a factor. The high ionization constant of the 2-carboxylic acid can be accounted for by the additional stabilization of the anion that would arise from intramolecular hydrogen bonding (III). Although no significant bonding of this type is found in the corresponding ester or in 2-acylpyrroles the greater polarizing power of the carboxylate anion might well result in an interaction of this type.

A similar effect is apparent in the alkaline hydrolysis of the esters of the pyrrole carboxylic acids. Although nucleophilic attack should be least favoured on the 2-carboxylate this isomer shows a higher reactivity than the 3-carboxylate. The adduct (IV) formed by the initial nucleophilic attack[26] contains a negatively charged oxygen atom which, as in the carboxylate anion, can interact with the imino group. The stabilization derived from this intramolecular bonding is apparently sufficiently great to allow this intermediate to be formed more readily than that from the

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[26] M. L. Bender, *Chem. Rev.* **60**, 53 (1960).

3-carboxylate. The generalization[27] that esters of pyrrole-2-carboxylic acids are hydrolysed more readily than the isomeric 3-carboxylates under alkaline conditions can be satisfactorily rationalized in these terms.

The high reactivity of ethyl pyrrole-1-carboxylate is entirely in accord with expectation. The carbonyl frequency of the ester and the general absence of amide properties for 1-acylpyrroles both indicate the low polarizibility of the pyrrole ring towards the 1-position and the effectively high electronegativity of the nitrogen atom.

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