

σ_I VALUES FOR ARYLUREIDO GROUPS

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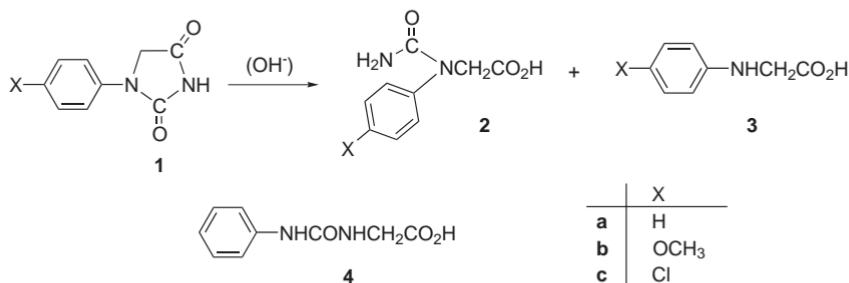
Dedicated to Professor Otto Exner on the occasion of his 80th birthday.

Three (1-arylureido)acetic acids were prepared by means of controlled alkaline hydrolysis of the respective 1-arylimidazolidin-2,4-diones. Their pK_a values and that of (3-phenylureido)acetic acid were determined potentiometrically by titration in 0.01 M solutions at 25.0 °C. Four new σ_I constants were calculated from the acidity constants.

Keywords: Hydantoin; *N*-Arylhydantoic acids; Acidity constants; Sigma values; *N*-Arylureido groups; Hammett equation; LFER.

There is a continued interest in σ constants related to the application of QSAR in drug design¹. In our study² of the mechanism of acyl transfer reactions by means of cyclizations of strained hydantoic acids, we encountered the need to estimate the pK_a values of the unstable tetrahedral intermediates using Hammett LFER³. These required as parameters σ_I values for substituted ureido groups. Exner and Lakomý⁴ have determined the σ_p and σ_m for the unsubstituted ureido group from the acidity constants of the respective benzoic acids. These have been used to calculate⁵ a field value for NHCONH_2 , $F = 0.09$. Charton's⁶ σ_I value of 0.23 for the ureido group is based on the hydantoic acid acidity constant. For substituted ureido groups we were forced to use estimates based on various assumptions². This prompted us to determine the σ_I values of some aryl substituted ureido groups which should presumably be of more general interest. The approach we chose was to use the acidity constants of (arylureido)acetic acids. Charton⁶ has shown that these are not affected significantly by steric effects.

We now report the synthesis of (1-arylureido)acetic acids, **2a–2c** (Scheme 1) and their potentiometrically determined acidity constants including that of (3-phenylureido)acetic acid (**4**). The acidity constants were used to calculate the σ_I values for the respective arylureido groups.



SCHEME 1

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. The ¹H NMR spectra were recorded in DMSO-*d*₆ at 250 MHz on a Bruker DRX 250 instrument. Chemical shifts are quoted in ppm (δ -scale) against TMS, coupling constants (*J*) are given in Hz. The IR spectra (in cm^{-1}) were recorded on an IFS 113 v instrument, UV spectra on a Specord UV/VIS spectrometer.

Materials

Inorganic reagents were of analytical grade and used without further purification. Potassium hydroxide solutions were prepared from CO_2 -free distilled water. 1-Arylimidazolidine-2,4-diones **1a–1c** were prepared according to Kochkanyan et al.⁷ giving literature m.p. values. Their structure and purity were confirmed by ¹H NMR spectra. (3-Phenylureido)acetic acid was prepared as described in⁸.

(1-Arylureido)acetic Acids **2**

Corresponding 1-arylhydantoin **1** (2 mmol) was dissolved in 5 ml of 0.8 M KOH. The hydantoin was hydrolyzed at 60 °C for 24 h. Upon cooling 1 M HCl was added dropwise to pH 6–7. The solution was left overnight in a refrigerator. The precipitate consisting of unchanged hydantoin was filtered off, the filtrate was acidified with 1 M HCl to pH 2 and the solution was left in refrigerator again. The hydantoic acid separated as white crystals was filtered off and crystallized from ethanol.

(1-Phenylureido)acetic acid (2a). Yield 53%; m.p. 160–161 °C. For $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_3$ (194.2) calculated: 55.67% C, 5.19% H, 14.43% N; found: 55.87% C, 5.15% H, 14.30% N. IR (KBr): 1719 (CO, COOH), 1633 (CO, NHCONH₂). ¹H NMR: 4.18 s, 2 H (CH_2); 5.76 s, 2 H (NH_2); 7.25–7.42 m, 5 H (Ar); 12.48 s, 1 H (OH).

[1-(4-Methoxyphenyl)ureido]acetic acid (2b). Yield 73%; m.p. 175–176 °C. For $C_{10}H_{12}N_2O_4$ (224.2) calculated: 53.57% C, 5.39% H, 12.49% N; found: 53.84% C, 5.48% H, 12.25% N. IR (KBr): 1716 (CO, COOH), 1631 (CO, NHCONH₂). ¹H NMR: 3.75 s, 3 H (OCH₃); 4.11 s, 2 H (CH₂); 5.60 s, 2 H (NH₂); 6.91–7.28 m, 4 H (Ar); 12.48 s, H (OH).

[1-(4-Chlorophenyl)ureido]acetic acid (2c). Yield 49%; m.p. 160–161 °C. For $C_9H_9ClN_2O_3$ (228.6) calculated: 47.28% C, 3.97% H, 12.25% N; found: 46.98% C, 3.87% H, 11.96% N. IR (KBr): 1694 (CO, COOH), 1650 (CO, NHCONH₂). ¹H NMR: 4.18 s, 2 H (CH₂); 5.92 s, 2 H (NH₂); 7.29–7.45 m, 4 H (Ar); 12.60 s, 1 H (OH).

Solubilities

In order to estimate the concentration at which titration in water would be possible, approximate solubilities of acids **2a–2c** were determined at ca. 4 °C by measuring the absorbances of the free acids after acidification of 0.03 M solutions of their potassium salts with 1 M HCl to pH 2 and filtering off the precipitate formed overnight in refrigerator. In calculating C_{sat} from the UV absorbances due to the arylureido group, the extinction coefficients determined for the K-salts were used (Table I).

TABLE I
UV spectral data and approximate solubilities at ca. 4 °C

Compound	λ_{max} , nm	ϵ , $\text{cm}^{-1} \text{ mol}^{-1} \text{ dm}^3$	C_{sat} , mol dm^{-3}
2a	235	3.77×10^3	0.025
2b	229	11.5×10^3	0.0083
2c	240	6.69×10^3	0.0096

pK_a Measurements

The pK_a values of the carboxy groups of the three (1-arylureido)acetic acids **2a–2c** and of (3-arylureido)acetic acid (**4**) were determined by potentiometric titration at 25 °C in a water jacket vessel under nitrogen⁹. The pH-meter used was a Radiometer pHM 84 Research pH-meter with a GK2401C electrode standardized at pH 7.00 and 4.01. The following procedure was used: 0.01 M stock solution of the potassium salt of the substituted hydantoic acid was prepared by dissolving equivalent amounts of the acid in 0.01 M potassium hydroxide. Aliquots of 20 ml were titrated with 5 ml 0.04 M HCl divided into 10 portions, the pH-meter readings becoming stable 10–15 s after each addition. No precipitate formation was observed during the titration up to 100% neutralization. The pK_a values were calculated after each addition of HCl,

$$pK = \text{pH} - \log ([A^-]/[AH]) , \quad (1)$$

deviated maximum ± 0.06 units from the average up to 90% neutralization. The averaged pK_a values were reproducible within 0.02 units.

RESULTS AND DISCUSSION

A versatile procedure for synthesis of hydantoic acids is alkaline hydrolysis of the respective hydantoins. In the case of hydantoic acids **2**, however, the parent hydantoins opened their ring only under rather severe treatment with aqueous alkali hydroxide solution, the main product being the anilinoacetic acids **3**. In the case of ureido acids **2a–2c** we could find conditions, such as those described in Experimental, under which substantial amounts of ureido acids could be isolated (50–70% after crystallization). This was done by fractional precipitation of the potassium salts from the solution obtained after hydrolysis. Hydantoins have $pK_a \approx 9$ for 3-H and should precipitate from solution at pH 6–7, after which the carboxylic acid was liberated at pH 2. At the latter pH apparently any anilinoacetic acid remained in solution as hydrochloride. Excess of mineral acid was avoided because of possible ready cyclization back to the parent hydantoin. The structure of the acids was supported by the spectral data presented above and their purity was checked by ^1H NMR.

Attempts to obtain 4-cyano and 4-nitro derivatives by the same procedure failed probably because of more ready hydrolysis at 2-C of hydantoin. Hydrolysis of the cyano group occurred as well.

The σ_I values were obtained using the parameters recommended by Charton⁶ assuming that our pK_a data at 0.01 mol dm⁻³ are not significantly different from the standard thermodynamic values

$$\sigma_I = -(pK_a - 4.76)/4.05 \quad (2)$$

Taking into account that the σ_I value for NHCONH_2 is 0.23 (based on a $pK_a = 3.8758$ for hydantoic acid)⁶ two conclusions from the data of Table II are apparent: (i) The field effect of *N*-phenyl substituents in both positions

TABLE II

The pK_a values^a of (1-arylureido)acetic acids **2** and (3-phenylureido)acetic **4** acid and σ_I values of arylureido groups

Compound	pK_a	Group	σ_I
2a	3.76 ± 0.01	$\text{C}_6\text{H}_5(\text{H}_2\text{NCO})\text{N}$	0.25
2b	3.78 ± 0.02	$4\text{-CH}_3\text{OC}_6\text{H}_4(\text{H}_2\text{NCO})\text{N}$	0.24
2c	3.63 ± 0.01	$4\text{-ClC}_6\text{H}_4(\text{H}_2\text{NCO})\text{N}$	0.28
4	3.80 ± 0.01	$\text{C}_6\text{H}_5\text{NHCONH}$	0.24

^a Mean values of at least two titrations.

of the ureido group on the acidity of hydantoic acid is quite small. This is not an expected result: σ_I of Ph itself is 0.25 and insulation by a single NH from $\text{CH}_2\text{CO}_2\text{H}$ in the case of adjacent substitution should bring down the contribution of Ph to ca. 0.1 (assuming additivity) and not the observed contribution of 0.02. The insensitivity to phenyl substitution is confirmed by almost the same σ_I value observed for the distant Ph substitution. (ii) The variations in σ_I for the 1-phenylureido, 1-(4-methoxyphenyl)ureido and 1-(4-chlorophenyl)ureido groups are also very small ($\Delta\sigma_I = 0.04$) but follow the pattern⁶ of variation of σ_I for $4\text{-XC}_6\text{H}_4$ with the same X substituents indicating that the observed differences are not accidental.

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