STUDIES IN PYRAZOLIDINE CHEMISTRY.

27.* STRUCTURE OF 4-YLIDENE-3,5-DIOXOPYRAZOLIDINES AND THEIR ACIDITY

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The Lewis acidity of 4-ylidene-3,5-dioxopyrazolidines decreases with increasing electron-donor capacity of the substituents in the para position of the 4-benzylidene residue and in the α-position of the exocyclic double bond. An analogous effect is found for the substituents in the 4-benzylidene residue on the NH-acidity of 1-phenyl-4-benzylidene-3,5-dioxopyrazolidines. The observed effect is analogous to their influence on the halfwave potential in the polarographic reduction on a dropping mercury electrode.

4-Ylidene-3,5-dioxopyrazolidines, which are used as intermediates in the preparation of anti-inflammatory agents [2], may display the properties of CH- and NH-acids as well as organic Lewis acids [1, 3, 4]. In this study, we compared their acidity with their structure and nature of the substituents in the heterocycle and in the 4-ylidene residue.

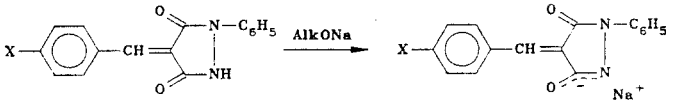
The compounds studied were 1,2-diphenyl- (I-XII) and 1-phenyl-2-methyl- (XIII, XIV), 4-arylidene- (I-IX, XII-XIV), and 4-heterolidene- (X, XI) 3,5-dioxopyrazolidines containing a polarized exocyclic double bond (group 1 compounds), 4-benzylidene-1-phenyl-3,5-dioxopyrazolidines (XV, XVI) containing an NH group in addition to the polarized double bond (group 2 compounds), 4-alkylidene- (XVII-XIX) and 4-cycloalkylidene- (XX, XXI) substituted 1,2-diphenyl-3,5-dioxopyrazolidines (group 3 compounds), and 4-alkylidene- (XXII) and 4-cycloalkylidene- (XIII, XXIV) 1-phenyl-3,5-dioxopyrazolidines (group 4 compounds) (see Table 1).

These compounds are insoluble in water and, thus, the pK_a values were determined by potentiometric titration by methanolic sodium methylate in DMF. A clear effect of the donor–acceptor nature of the substituent in the para position of the 4-benzylidene residue on the pK_a value is observed in group 1 compounds both for the 1,2-diphenyl and 1-phenyl-2-methyl derivatives. The pK_a values in this series correlate satisfactorily with the σ_{para} substituent constants according to Jaffe, McDaniel, and Brown [5]: $pK_a = 11.884 - 3.316\sigma_p$, $r = 0.953$. The substitution of more electron-donor residues in the benzylidene residue of I, namely phenylethylene (IX), anthryl (X), and furyl groups (XI), leads to a significant decrease in acidity (from 11.0 to 13.7).

A decrease in acidity with an increase in the electron-donor effect of the substituent in the α-position in going from the p-nitrophenyl derivative (XIX) to the phenyl (XVIII) and methyl derivatives (XVII) is also observed in the 4-alkylidene-1,2-diphenyl series.

An increase in acidity is observed with an increase in the electron-withdrawing nature of the substituent at the nitrogen atom upon the sequential replacement of CH_3 by H and C_6H_5 (compounds XIII, XV, and I). The same effect is found for the p-nitrophenyl derivatives (XIV), (XVI), and (XIX), by the pK_a values of these compounds are less than those for the preceding series due to the electron-withdrawing effect of the nitro group. The data given on the effect of the substituent at the nitrogen atom are in good accord with the transition from 1-phenyl- (XXV) to 1,2-diphenyl-3,5-dioxopyrazolidine (XXVI).

We should note that group 3 compounds (XV) and (XVI) react with sodium alcoholate as an NH-acid [1]:



*For Communication 26, see [1].

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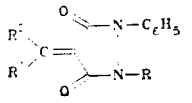
TABLE 1. pK_a Values of 4-Alkylidene-3,5-dioxopyrazolidines

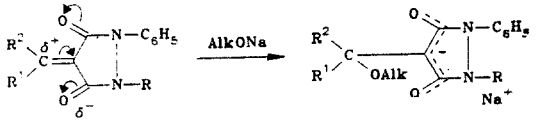


Compound*	R²**	E, mV	pK_a	Compound*	R²**	E, mV	pK_a
I	C_6H_5	−194,7	11,0	XIV	4-$O_2NC_6H_4$	−200,6	11,1
II	4-$(CH_3)_2NC_6H_4$	−390,5	14,3	XV	C_6H_5	−212,4	11,3
III	4-$H_2NC_6H_4$	−380,5	14,15	XVI	4-$O_2NC_6H_4$	−162,2	10,5
IV	4-$CH_3OC_6H_4$	−303,8	12,85	XVII	CH_3	−288,6	12,6
V	3,4-$(CH_3O)_2C_6H_3$	−336,0	13,4	XVIII	C_6H_5	−107,7	9,5
VI	$(CH_3)_3N^+C_6H_4$	−94,4	9,3	XIX	4-$O_2NC_6H_4$	−47,2	8,4
VII	4-$CH_3CONHC_6H_4$	−321,5	13,2	XX		−136,7	11,0
VIII	4-$O_2NC_6H_4$	−59,0	8,7	XXI		−336,2	13,4
IX	$C_6H_5CH=CH$	−361,6	13,8	XXII	CH_3	−288,6	12,6
X	Anthryl	−353,0	13,63	XXIII		−224,2	11,5
XI	2-Furyl	−353,9	13,7	XXIV		−218,3	11,4
XII	C_6H_5	−353,9	13,7	XXV		−212,4	11,3
XIII	C_6H_5	−348,0	13,6	XXVI		−76,7	9,0

* I—XII, XVII—XXI R=C_6H_5, XIII, XIV R=CH_3, XV, XVI, XXII—XXIV R=H; I—XI, XIII—XVI R^1=H, XII R^1=C_6H_5, XVII—XIX, XXII R^1=CH_3.

** XX, XXIII $R^1+R^2=(CH_2)_4$; XXI, XXIV $R^1+R^2=(CH_2)_5$; XXV $R+R^1+R^2$= 1-phenyl-3,5-dihydroxypyrazolidine; XXVI $R+R^1+R^2$= 1,2-diphenyl-3,5-dihydroxypyrazolidine.

Thus, all the substituents at both the heterocycle nitrogen atom and at the α-position of the 4-ylidene residues in the 4-ylidene-1,2-disubstituted 3,5-dioxopyrazolidines, which increase the polarization of the exocyclic double bond and thereby decrease the electron density on the α-carbon atom, leads to an increase in their acidity in the following reaction:



The substitution of the hydrogen in the α-position by an electron-withdrawing residue in going from I to XII leads to a significant decrease in acidity, which is apparently a consequence of steric blocking of the exocyclic double bond, which hinders the approach of the alkoxy group. The reduced acidity of the sterically more hindered 4-cyclohexylidene derivative (XXI) in comparison with the 4-cyclopentylidene derivative (XX) may be ascribed to the same effect.

It was of interest to compare the effect of substituents in the 4-benzylidene residue on pK_a with their effect on the position of the half-wave potential in polarographic reduction, which may be considered as the nucleophilic addition of electrons. During polarographic reduction of 4-ylidene-3,5-dioxopyrazolidines in DMFA at a mercury-drop electrode described earlier [6] there are polarographic waves from −0.4 to −0.96 V with a height corresponding to the transition of one electron per molecule. The position of this wave is shifted toward negative potential values upon introducing electron-donor substituents into the benzylidene residue and also in going from α-phenylethylidene derivative (XVIII) to 4-α-methylethylidene derivative (XVII). This wave is apparently a result of the one-electron reduction of the exocyclic double bond since it is lacking in the reduction of the corresponding saturated compounds such as 4-benzyl-1,2-diphenyl-3,5-dioxopyrazolidine ($E_{1/2}$ = 1.78 V). In this case, a satisfactory correlation is also observed, which supports the described features of the relationship of structure and acidity of 4-ylidene-3,5-dioxopyrazolidines, $E_{1/2} = 0.5177-0.188\sigma_p$, r = 0.93.

EXPERIMENTAL

The syntheses of I-XXVI were described in our previous work [1, 2, 7, 8].

Procedure for the Potentiometric Determination of pK_a. Solutions of the compounds studied (c ≈ 2 mmoles/liter) were prepared in DMF. This DMF sample was dried over 120 h using calcium oxide freshly roasted at 1100°C and then distilled twice in vacuum in a dry

nitrogen atmosphere. For the potentiometric titration we used a circuit consisting of a glass electrode and silver chloride electrode with potassium chloride saturated in methanol. The glass electrode was first immersed in 0.1 N aqueous hydrochloric acid over 24 h and then for about this duration in distilled water, while it was immersed prior to operation in DMF for about 1 h. Measurement of the electromotive force of the circuit in a buffer solution consisting of benzoic acid and sodium benzoate ($c_{acid} = c_{salt} = 1$ mM) was used to follow the state of the glass electrode. A weighed sample of the compound studied was dissolved in 15 ml DMF. Then, 1 eq. 0.01 N sodium methylate solution was added. The mixture was thoroughly stirred using a magnetic stirrer and the pH was measured thrice on a 362 pH-meter. Benzoic acid, which was used as the standard, was titrated with sodium methylate under analogous conditions.

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CATALYTIC REDUCTION OF 4-(3-OXOQUINUCLIDYL-2-METHYLIDENE)-6-METHOXYQUINOLINE AND ITS ETHYLENEKETAL

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An examination was carried out on the catalytic reduction of 4-(3-oxoquinuclidyl-2-methylidene)-6-methoxyquinoline, its ethyleneketal, and the ethyl ester of 6-(3,4-dimethoxystyryl)picolinic acid. Stepwise nature was shown for the hydrogenation of the pyridine and quinoline rings, side chains, and catalytic demethoxylation using PMR spectroscopy, mass spectrometry, and gas–liquid chromatography.

In a search for new cardiovascular drugs, we studied the catalytic reduction of possible intermediates in their synthesis, namely 4-(3-oxoquinuclidyl-2-methylidene)-6-methoxyquinoline (I) and its ethyleneketal (V). PMR spectroscopy, mass spectrometry, and gas–liquid chromatography were used to study the stepwise hydrogenation of the exocyclic double bond and the different fragments and the catalytic demethoxylation (see scheme at top of following page).

Quinoline (I) was obtained according to Bender [1] by the condensation of 3-quinuclidone with quinaldehyde and its structure was confirmed by PMR spectroscopy (Table 1). Similarly to analogously synthesized 2-arylidene- and 2-heteroarylidene-3-oxoquinuclidines [2-4], I is

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