THE REACTIVITY OF SUBSTITUTED 6,9-DICHLORACRIDINES

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Key words: 6,9-dichloracridine, reactivity; acid-base balance; associated acids; Hammet equation; principle of available energy linearity; donor substituents; acceptor substituents; correlative equations

The constants of ionization \( pK_{\text{act}} \) of substituted 6,9-dichloracridines have been determined in the mixed ethanol – water solvent (50 mole percent of ethanol) at the temperature of 25°C by the method of potentiometric titration. It has been shown that these compounds are weak bases (\( pK_{\text{act}} \) of the corresponding associated acids is in the range of 3.71-3.95). It has been proven that their basicity depends upon the nature and position of substituents in the heterocycle. Introduction of 9-chlorine substituent to the molecule of acridine leads to significant weakening of basic properties (\( pK_{\text{act}} ^- = 0.82 \)) due to decrease of the electron density on the atom of nitrogen (reactive centre). The appearance of 9-chloracridine of chlorine atoms in the molecule in 2-, 4-positions also decreases basicity of the heterocycle, but approximately 6.5 times less (\( pK_{\text{act}} ^- = 0.13 \) (2-Cl), \( pK_{\text{act}} ^- = 0.14 \) (4-Cl)). On the contrary, the donor substituents increase basicity. The quantitative assessment of the substituents influence has been performed within the principle of available energy linearity according to the Hammet equation by the correlation analysis method. The equation obtained, which includes \( pK_{\text{act}} ^- \) of all experimental compounds, proved to be statistically uncertain. On the plot of \( pK_{\text{act}} ^- \) – \( f(\sigma) \) dependence, the value of \( pK_{\text{act}} ^- \) for 4-methoxy substituted is supposed to be out of the linear dependence. Elimination from correlation of \( pK_{\text{act}} ^- \) for 4-methoxy substituted 6,9-dichloracridine allowed to obtain the correlation equation of \( pK_{\text{act}} ^- \) – \( f(\sigma) \) relationship with reliable statistic characteristics. This equation allows to predict reactivity of other members of this homologous series. The low value of the reaction constant is \( \rho = 0.86 \) and testifies a slight sensitivity of the reactive centre (heterocyclic atom of nitrogen) to the influence of substituents in the molecule of substituted 6,9-dichloracridine. It is notable that the reactive constants \( \rho \) for 6,9-dichloracridines, 5-nitro-9-chloracridines within the limits of experimental error coincide, and it indicates the single mechanism of the electronic influence of substituents on the reactive centre.

Substituents of 9-chloracridine are widely used as starting substances for obtaining various biologically active 9-amino-, 9-alkylamino-, 9-arylamino-, 9-hydrazoneacridines [3-5, 8-12, 16, 18-20]; markers in genetic engineering [6]; luminescent indicators in analytical chemistry [6, 15, 17].

The aim of the research is to study reactivity of substituted 6,9-dichloracridines because the reactivity of compounds of this homologous series has not been investigated in details [5, 12]. Thus, the relevance of the research is beyond a doubt as it allows to optimize the synthesis of these compounds.

The reactivity of this class of compounds has been investigated by the study of the acid-base balance (Scheme).

The ionization constants (\( pK_{\text{act}} ^- \)) of acids associated with substituents of 6,9-dichloracridine in the mixed solvent such as ethanol–water (50 mole percent of ethanol) have been determined by the method of potentiometric titration at the temperature of 25°C (Table).

These data testify that substituted 6,9-dichloracridines are weak bases; \( pK_{\text{act}} ^- \) of the corresponding associated acids are in the range of 3.71-3.95. Basicity of substituted 6,9-dichloracridines depends on the nature and position of substituents in the heterocycle. Introduction of 9-chlorine substituent to the molecule of acridine leads to significant weakening of basic properties (\( pK_{\text{act}} ^- = 0.82 \) [13] due to decrease of the electron density on the atom of nitrogen (reactive centre). The appearance of 9-chloracridine of chlorine atoms in the molecule in 2-, 4-positions also decreases basicity of the heterocycle, but approximately 6.5 times less (\( pK_{\text{act}} ^- = 0.13 \) (2-Cl), \( pK_{\text{act}} ^- = 0.14 \) (4-Cl)). On the contrary, the donor substituents increase basicity.

The quantitative assessment of the substituents influence has been performed within the principle of available energy linearity according to the Hammet equation by the correlation analysis method. The equation obtained (1) is statistically uncertain because of the low value of the correlation coefficient (r):

\[
pK_{\text{act}} ^- = (3.85 \pm 0.04) - (0.50 \pm 0.09) \sigma \quad (1)
\]

\[
\begin{align*}
\text{n} & = 9 \\
\text{r} & = 0.845 \\
\text{s} & = 0.016
\end{align*}
\]
On the plot of \( \text{pK}_{\text{sub}}^+ - f(\sigma) \) dependence (Fig.) the values of \( \text{pK}_{\text{sub}}^+4^- \) for 4-methoxy substituent are out of the linear dependence. The same effect is observed when studying 5-nitro-9-chloracridines [5], 9-thioacridones [10], 9-hydrazineacridines [11]. Probably it is connected with the intramolecular hydrogen bonding between oxygen of 4-methoxy group and heterocyclic nitrogen.

Elimination from correlation of \( \text{pK}_{\text{sub}}^+ \) for 4-methoxy substituted 6,9-dichloracridines (3) leads to sharp improvement of statistical characteristics:

\[
\text{pK}_{\text{sub}}^+ = (3.86 \pm 0.02) - (0.86 \pm 0.05) \cdot \sigma \\
\text{r}=0.989 \quad s=0.016
\]  

The low value of the reaction constant \( \rho = 0.86 \) testifies a slight sensitivity of the reactive centre (heterocyclic atom of nitrogen) to the influence of substituents in the molecule of substituted 6,9-dichloracridine. It is interesting to note that reactive constants \( \rho \) for 6,9-di-chloracridines [5], 5-nitro-9-chloracridines [5] within the limits of experimental error coincide, and it indicates the single mechanism of the electronic influence of substituents on the reactive centre.

**Experimental Part**

The study of the acid-base balance was performed by the method [1]. The titrant was 0.01 M aqueous solution of hydrochloric acid. The concentration of the solutions to be titrated was 0.005 mol/dm\(^3\) in the point of semi-neutralization. Potentiometric titration was performed on an EV-74 ionomer using glass (ESP-43-074) and silver chloride (EVP-1M) electrodes at 25°C. The experiments were carried out in triplicate, and the data obtained were analyzed according to the requirements of the SPHU [2]. The correlative analysis was conducted by methods of mathematic statistics (with the confidence interval of 0.95) [7].

In order to prepare the mixed solvent, the bidistillate free of CO\(_2\) and ethanol were used.
Properties of substituted 6,9-dichloracridines (1-9)

| Compound | Yield, % | Melting point, °C | Found, % | Molecular formula | Calculated, % | pK_{BH} | N | C | H |
|----------|---------|-------------------|----------|-------------------|---------------|----------|---|---|---|
| 1        | 96      | 100-101           | 5.64     | C_{9}H_{12}Cl_{2}N | 5.65         | 62.93    | 2.84 | 3.85±0.02 |
| 2        | 93      | 123-125           | 5.05     | C_{9}H_{12}Cl_{2}NO | 5.04         | 60.46    | 3.26 | 3.94±0.04 |
| 3        | 95      | 119-121           | 5.03     | C_{9}H_{12}Cl_{2}NO | 5.04         | 60.46    | 3.26 | 3.95±0.04 |
| 4        | 92      | 129-132           | 5.33     | C_{9}H_{12}Cl_{2}N  | 5.34         | 64.15    | 3.46 | 3.92±0.01 |
| 5        | 90      | 127-129           | 5.35     | C_{9}H_{12}Cl_{2}N  | 5.34         | 64.15    | 3.46 | 3.89±0.03 |
| 6        | 94      | 98-100            | 4.95     | C_{9}H_{12}Cl_{2}N  | 4.96         | 55.26    | 2.14 | 3.72±0.03 |
| 7        | 93      | 99-101            | 4.95     | C_{9}H_{12}Cl_{2}N  | 4.96         | 55.26    | 2.14 | 3.71±0.02 |
| 8        | 91      | 133-135           | 5.08     | C_{9}H_{12}Cl_{2}N  | 5.07         | 65.24    | 4.01 | 3.95±0.03 |
| 9        | 90      | 137-139           | 5.06     | C_{9}H_{12}Cl_{2}N  | 5.07         | 65.24    | 4.01 | 3.94±0.04 |

The synthesis of substituted 6,9-dichloracridines (1-9) was carried out by the method [14]; their physical and chemical parameters corresponded to the literature data [14].

CONCLUSIONS
1. The reactivity of substituted 6,9-dichloracridines has been researched in the reverse conditions by studying the acid-base balances of the corresponding associated acids in the mixed ethanol – water solvent (50 moles percent of ethanol) at 25°C.
2. The influence of the nature and position of substituents in the heterocycle upon the strength of the corresponding associated acids has been analyzed.
3. It has been proven that acceptor substituents weaken basicity of 6,9-dichloracridine, but donor substituents cause the opposite effect.
4. The Hammet correlation equation has been obtained with convincing statistic characteristics; it is used to predict acid-base properties of substituted 6,9-dichloracridines.

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РЕАКЦИОННАЯ СПОСОБНОСТЬ ЗАМЕЩЕННЫХ 6,9-ДИХЛОРПРОПИДИНОВ
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Ключевые слова: 6,9-дихлорпиримидин; реакционная способность; кислотно-основные равновесия; сопряженные кислоты; уравнение Гаммета; принцип линейности свободных энергий; донорные заместители; акцепторные заместители; корреляционные уравнения.

Определены константы ионизации рН± для замещенных 6,9-дихлоракридина в смешанном растворителе этанол-вода (50 мольных % этанола) при 25 °C методом потенциометрического титрования. Показано, что эти соединения - слабые основания (рKb± соответствующих сопряженных кислот находится в пределах 3,71-3,95). Доказано, что их основность зависит от природы и положения заместителей в гетероцикле. Введение в молеклу 9-хлорзаместителя приводит к существенному ослаблению основных свойств (рKb± = 0,82) вследствие уменьшения электронной плотности на атоме азота (реакционный центр).

Исключение из корреляции рKb± для 4-метоксизамещенного 6,9-дихлоракридина приводит к корреляционному уравнению, которое позволяет прогнозировать реакционную способность других членов этого гомологического ряда. Небольшое значение реакционной константы ρ = 0,86 свидетельствует о невысокой чувствительности реакционного центра к влиянию заместителей в молекуле замещенных 6,9-дихлоракридина.

Интересно отметить, что реакционные константы ρ для 6,9-дихлоракридина, 5-нитро-9-хлоракридина в пределах ошибки эксперимента совпадают, что указывает на единую реакционную способность заместителей в гетероцикле.