UDC 547. 792+547. 796+543. 257. 1+543. 422+542. 95

RESEARCHES ON 1, 2, 4-TRIAZOLES

VII. Properties and Reactions of 1, 2, 4-Triazolinones and 1-Aryltetrazolinones(5)*

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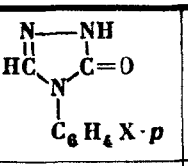
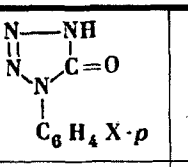
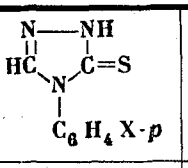
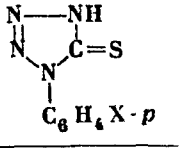
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 4, pp. 580-585, 1965

Determination of the acidity constants of 1-aryltetrazolinethiones-5, 4-aryl-1, 2, 4-triazolinethiones-3, 1-aryltetrazolinones-5, 4-aryl-1, 2, 4-triazolinones-3 shows that carbonyl compounds are 10^{-1}-10^{-2} times less acid than compounds with a thione group. Acidities are found to increase considerably, 10^{3}-10^{4} times, on passing from triazole compounds to tetrazole ones. 4-Aryl-1, 2, 4-triazolinones-3 and 1-aryl-tetrazolinones-5 are aminomethylated and cyanoethylated and the reactions found to take place at the amide nitrogen atom.

Continuing a comparison of properties of triazole and tetrazole compounds, the problem now set was to study the changes in properties of compounds where, in 4-aryl-1, 2, 4-triazolinethiones-3 (TRIT) and 1-aryltetrazolinethiones-5 (TETT), the thione group replaced carbonyl, and to compare these compounds with 4-aryl-1, 2, 4-triazolinones-3 (I), and 1-aryltetrazolinones-5 (II). As was demonstrated in the preceding paper, compounds I and II readily give the corresponding sulfones on hydrolysis [1]. The azolinones I and II prepared are colorless crystalline compounds which are usually alkali-soluble, and male higher than the corresponding sulfur analogs. The IR spectra of I and II have a marked

Table 1

Acidity Constants of TRIT and TETT

X				
H	$1.20 \cdot 10^{-9}$	$1.78 \cdot 10^{-5}$	$1.58 \cdot 10^{-7}$	$2.24 \cdot 10^{-4}$ [3]
Cl	$1.58 \cdot 10^{-9}$	$2.34 \cdot 10^{-5}$	$2.51 \cdot 10^{-7}$	$2.40 \cdot 10^{-4}$ [3]
OC_2H_5	$7.94 \cdot 10^{-10}$	$1.00 \cdot 10^{-5}$	$6.31 \cdot 10^{-8}$	—

absorption band in the 1715-1700 cm^{-1} region, due to valence vibration of the carbonyl group. In the 3210-3180 cm^{-1} region there is the NH group valence vibration absorption band, the group apparently being involved in intermolecular hydrogen bonding with the carbonyl group. A lactam structure for these compounds is indicated by the presence of the carbonyl band and the absence of an OH band in the 3600-3500 cm^{-1} region.

Acidity constants were determined for the purpose of comparing the mobilities of the protons in TRIT and TETT with those in the corresponding azolinones I and II. It is known, for example, that thioacetic acid is a stronger acid than acetic acid [2]. The analogous compounds TRIT and TETT were stronger acids than the azolinones I and II (Table I). K_α for the triazole compounds was found in water, for the tetrazole ones in 50% ethanol. In water K_α TETT is $2.82 \cdot 10^{-3}$.

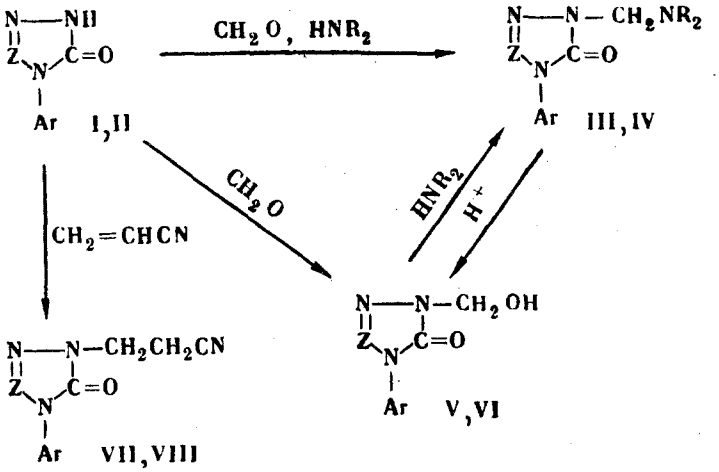
Comparison of the K_αs of triazole compounds with those of the corresponding tetrazole compounds is of interest. The Table shows that the acidities of the tetrazolines were 10^{3}-10^{4} times greater than those of the triazolines. Here the part played by the quaternary ring (doubly-linked) nitrogen atom in TETT in comparison with TRIT is obvious.

Regarding the effect of substituents in the phenyl moiety on K_α, a para chlorine atom has an electron-accepting effect and increases acidity, the electron-donor ethoxy group, on the other hand, substantially lowering the acidities of triazole and tetrazole compounds.

Replacement of the thione groups in TRIT and TETT by carbonyl groups, as in compounds I and II, inevitably affected the chemical properties of these compounds. To ascertain the extent to which this occurs, the reactions carried out with TRIT and TETT [4-7] were also carried out with the azolinones I and II. The latter readily undergo the Mannich

*For Part VI see [1].

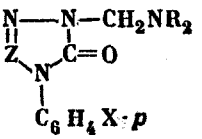
reaction, giving good yields of aminomethyl derivatives derived from the amide nitrogen (Table 2). The Mannich bases (III, IV) are colorless substances, readily soluble in organic solvents, but insoluble in water.



I, III, V, VII Z=CH
II, IV, VI, VIII Z=N

Table 2

Aminomethylation Products III, IV



X	Z	NR_2	Mp, °C	Formula	N, % Found	N, % Calculated	Appearance of crystals	% yield
H	CH	Piperidyl	140—141	$C_{14}H_{18}N_4O$	21.51	21.69	Needles	85
H	CH	Hexamethyleneimino	152—153	$C_{15}H_{20}N_4O$	20.91	20.57	Needles	95
Cl	CH	Piperidyl	159—160.5	$C_{14}H_{17}N_4OCl$	19.15[a]	19.14	Needles	83
Cl	CH	Diethylamino	110—110.5	$C_{13}H_{17}N_4OCl$	20.37	19.96	Plates	80
Cl	CH	Morpholyl	183—184.5	$C_{13}H_{15}N_4O_2Cl$	19.01b	19.01	Needles	93
Cl	CH	Hexamethyleneimino	145—145.5	$C_{15}H_{19}N_4OCl$	18.63c	18.26	Needles	89
OC_2H_5	CH	Diethylamino	89—91	$C_{15}H_{22}N_4O_2$	19.59	19.30	Plates	60
OC_2H_5	CH	Hexamethyleneimino	105—106	$C_{17}H_{24}N_4O_2$	18.03d	17.71	Needles	88
OC_2H_5	CH	Pyrrolidyl	104—105	$C_{15}H_{20}N_4O_2$	19.53	19.43	Needles	82
H	N	Piperidyl	48—50	$C_{13}H_{17}N_5O$	27.02	27.01	Plates	53
H	N	Morpholyl	118—119	$C_{12}H_{15}N_5O_2$	27.04	26.80	Plates	79
Cl	N	Morpholyl	105—106	$C_{12}H_{14}N_5O_2Cl$	23.87	23.68	Plates	84
Cl	N	Piperidyl	76—77	$C_{13}H_{16}N_5OCl$	23.85	23.84	Plates	72

a) Found: Cl 12.04%. Calculated: Cl 12.11%.
b) Found: Cl 11.74%. Calculated: Cl 12.03%.
c) Found: Cl 11.33%. Calculated: Cl 11.56%.
d) Found: C 64.34; H 7.67%. Calculated: C 64.53; H 7.64%.

Heating the Mannich bases III with acetic acid hydrolyzes them to the hydroxymethyl derivatives V, which can also be prepared by heating the azolinones I with formaldehyde. The hydroxymethyl derivative VI* is unstable, cold water decomposing it slowly to the starting tetrazolinone II. Consequently heating the tetrazoline Mannich bases IV

*Stolle [8] first obtained this compound, but he mistakenly considered it to be a tetrazole derivative containing the group $-OCH_2OH$ (cf. [6]).

with dilute acetic acid does not result in hydrolysis to hydroxymethyl derivatives, as it does in the case of the tetrazoline-derived Mannich bases III, but immediately gives the tetrazolinone II. Mannich bases are formed when the hydroxymethyl derivatives V and VI react with amines. UV spectra of Mannich bases III, IV and hydroxymethyl derivatives V show λ_{max} 237-242 mμ in the case of triazole derivatives, and λ_{max} 245-250 for tetrazole ones. These data agree well with those for compounds I and II (Figs. 1 and 2). The correspondences between the maxima, and the character of the curves show in aminomethylation, where substitution occurs at the nitrogen of the amide group.

1-Phenyltetrazolinone-5 (II) reacts with β-chloropropionitrile to give an N-cyanoethyl derivative, but it was not possible to alkylate 4-phenyl-1, 2, 4-triazolinone-3 (I) with β-chloropropionitrile. 4-Phenyl-1, 2, 4-triazolinone-3 (I) and 1-phenyl-tetrazolinone-5 (II) were also cyanoethylated. However, the azolinones I and II do not react under conditions such that TRIT and TETT readily react with acrylonitrile (sodium ethoxide in dioxane-alcohol). This once again

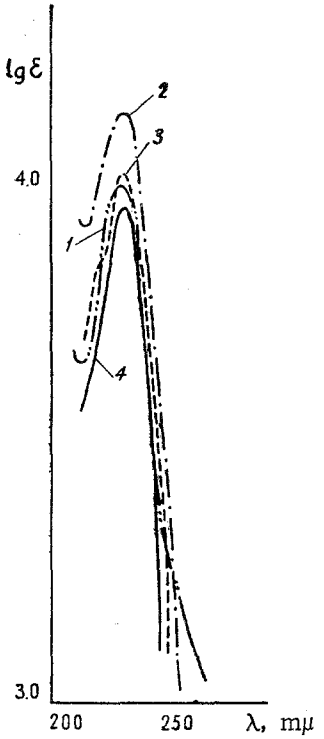


Fig. 1. UV absorption spectra (in ethanol): 1) 4-Phenyl-1, 2, 4-triazolinone-3; 2) 4-Phenyl-2 piperidinomethyl-1, 2, 4-triazolinone-3; 3) 4-Phenyl-2 hydroxymethyl-1, 2, -4 triazolinone-3; 4) 4-Phenyl-2-β-cyanoethyl-1, 2, 4-triazolinone-3

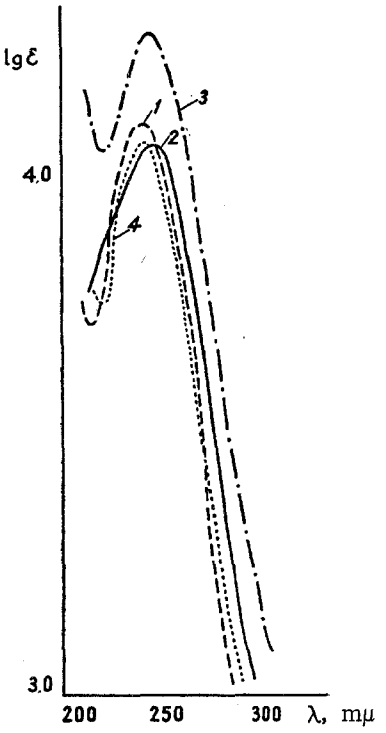


Fig. 2. UV absorption spectra (in ethanol): 1) 1-Phenyl-tetrazolinone-5; 2) 1-Phenyl-4-morpholinomethyltetrazolinone-5; 3) 1-Phenyl-4-β-cyanoethyltetrazolinone-5; 4) 1-Phenyl-4-hydroxymethyltetrazolinone-5

shows that azolinones are of less acidic character than azolinethiones. More drastic conditions are required for the cyanoethyl moiety to enter azolinones I and II: reaction with excess acrylonitrile and dry alkali as the catalyst. With a tetrazolinone this method of cyanoethylation gives a low yield (7%). The UV spectra show (Figs. 1, 2) that both compounds cyanoethylate to N-cyanoethyl derivatives, and that O-derivatives are not formed.

Figures 1 and 2 show that the UV absorption spectra curves of the triazole compounds investigated look just like those of the tetrazole compounds. However, λ_{max} for the latter is slightly (5 mμ) displaced towards the longer wavelengths, possibly because of greater equalization of electron density in the tetrazole ring than in the triazole one.

Experimental

Aminomethylation of azolinones I and II. 0.002 mole 4-aryl-1, 2, 4-triazolinone-3 (I) or 1-aryltetrazolinone-5 (II) was dissolved in 4 ml methanol and 0.0023 mole amine. 0.25 ml formalin was then added at room temperature. Usually a precipitate of the aminomethyl derivative separated after standing for a short time, it was filtered off, washed with ether, and crystallized from 30% aqueous methanol. The products were very soluble in all organic solvents, but insoluble in water

4-Phenyl-2 hydroxymethyl-1, 2, 4-triazolinone-3 (V).

a) 0.16 g 4-phenyl-1, 2, 4-triazolinone-3 was refluxed with 3 ml formaldehyde solution until solution was complete, cooled, and the resultant precipitate filtered off. Yield 0.15 g (79%), needles, mp 195-195.5° (from water).

Found: N 21.97%. Calculated for $C_9H_9N_3O_2$: N 21.98%.

b) Hydrolysis of the Mannich base. 0.27 g 4-phenyl-2 hexamethyleneiminomethyl-1, 2, 4-triazolinone-3 was heated to boiling with 10 ml 10% acetic acid, and the precipitate formed on cooling filtered off. Yield 0.14 g (74%), needles from water, mp 195-195.5°.

According to the literature 1-phenyl-4-hydroxymethyltetrazolinone-5 has mp 74° [8].

4-Phenyl-2-hexamethyleneiminomethyl-1, 2, 4-triazolinone-3. 0.19 g 4-phenyl-2-hydroxymethyl-1, 2, 4-triazolinone-3 was dissolved in 5 ml methanol and 0.2 ml hexamethyleneimine added. The precipitate of Mannich base which separated after shaking for a short time was filtered off and recrystallized from 30% aqueous methanol. The product was identical with the Mannich base made by direct aminomethylation (see above).

4-Phenyl-2-β-cyanoethyl-1, 2, 4-triazolinone-3 (VII). 0.8 g 4-phenyl-1, 2, 4-triazolinone-3 was rubbed in a mortar with 0.05 g solid sodium hydroxide, the mixture suspended in 4 ml acrylonitrile, and kept for 10 hr at 45-50°. 20 ml water was added to the resultant solution, the upper layer separated off, and the acrylonitrile distilled off under vacuum. The precipitate of cyanoethyl compound which formed was filtered off and recrystallized from water. Yield 0.90 g (85%), mp 100-102° (needles). Found: C 61.96; H 4.81; N 26.15%. Calculated for $C_{11}H_{10}N_4O$: C 61.67; H 4.70; N 26.15%.

1-Phenyl-4-β-cyanoethyltetrazolinone-5 (VIII).

a) 1.62 g 1-phenyltetrazolinone-5 was rubbed in a mortar with 0.2 g solid sodium hydroxide, the mixture suspended in 1.98 ml freshly-distilled acrylonitrile, and the whole held at 55-60° for 4 hr. 25 ml water was then added, the oily precipitate separated, treated with ether, filtered off, and recrystallized from alcohol. Mass 0.15 g (7%), mp 93-95° (prisms). Found: N 32.63%. Calculated for $C_{10}H_9N_5O$: N 32.53%.

b) 0.81 g 1-phenyltetrazolinone-5 was heated for 2 hr with 0.5 ml β-chloropropionitrile and 3 ml 2N sodium hydroxide. The precipitate of cyanoethyl derivative V which separated after cooling was filtered off, and recrystallized from alcohol. Yield 0.82 g (76%), mp 93-95° (prisms).

Acidity constants were determined by potentiometric titration with 0.1 N sodium hydroxide solution using a hydrogen electrode against a saturated calomel one. As usual, the pH at half neutralization was found from the plot, this corresponding to pK_α. All the tetrazole derivatives were titrated in 50% alcohol, while the triazole compounds were titrated in water.

IR spectra were determined with an IKS-14 instrument, mixes with vaseline being used in the range 1800-1300 cm^{-1}, and with perfluoro hydrocarbons in the range 3600-2000 cm^{-1}.

The IR spectra of the 1-aryltetrazolinones-5 were (given: aryl group, NH absorption band, carbonyl absorption band): phenyl, 3174 medium, 1706 very weak; p-chlorophenyl, 3100 medium, 1680 and 1713 very weak; p-ethoxyphenyl, 3183 medium, 1706 very weak.

IR spectra of 4-aryl-1, 2, 4-triazolinones-3 (given: aryl group, NH absorption band, carbonyl absorption band): phenyl, 3200 medium, 1706 very weak; p-chlorophenyl, 3208 medium, 1704 and 1714 very weak; p-ethoxyphenyl, 3185 medium, 1701 very weak.

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14 July 1964

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