KETIMINE-ENAMINE TAUTOMERS OF TETRAZOLO[1,5-*a*]QUINOXALINE DERIVATIVES*

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4-Ethoxycarbonylmethylene-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline and its α-substituted derivative display ketimine-enamine tautomeric isomerism. Their IR spectra and hydrazinolysis of 3,4-dihydro-3-oxo-quinoxaline analogues and related substances were studied.

Tetrazolo[1,5-*a*]quinoxalines, synthetically accessible *via* 2-hydrazino derivatives of quinoxaline, have been patented for their herbicidal activity[1]. Now, we tried to extend our investigations concerning 2-ethoxycarbonylmethylene-3-oxo-1,2,3,4-tetrahydroquinoxaine (*I*) and its derivatives and to prepare tetrazoloquinoxaline analogues.

2-Hydrazino-3,4-dihydro-3-oxoquinoxaline[2] (*II*) was prepared in a different manner. While ester *I* on reaction with hydrazine gives the expected hydrazide[3], its α-phenyl derivative, *i.e.* ethyl (3,4-dihydro-3-oxo-2-quinoxalinyl)phenyl acetate (*III*) afforded a different product. In the course of the reaction ethyl phenyl acetate is formed which on reaction with an excess of hydrazine is converted to phenylacethydrazide. From the reaction mixture we isolated a second product to which we assigned the structure of hydrazino derivative *II* on the basis of its elemental composition and IR spectrum.

We also submitted to hydrazinolysis the structurally related ethyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)propanoate (*IV*) with the ketimine tautomeric structure which gave corresponding hydrazide *V*, similarly as ester *I*. Although we did not study the kinetics of these reactions we consider that the different centre of the nucleophilic attack of hydrazine in ester *III* is determined by the resonance stabilization of ethyl phenylacetate carbanion as the leaving group. For the explanation of the mechanism of hydrazinolysis of ester *I* it is not necessary to take enamine-ketimine tautomeric isomerization into consideration, because according to our present results with kinetic measurements it takes place very rapidly in alkaline medium[4]. In contrast to the reaction with hydrazine the hydrolysis of ester *III* in alkaline medium takes

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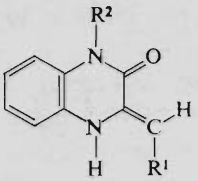
place on the carbonyl carbon of the ester group[3], in consequence of a lower nucleophility of the reagent. The reaction of 1,2-diaminobenzene with 2-ethoxalylcyclohexanone may also be classified to the hydrazinolysis of ester *III* which represents the reversible reaction of the ester condensation of ethyl oxalate. From the reactions in acetic acid, ethyl acetate and ethanol, and under the conditions of acid and base--catalysis. or even when the reaction was carried out without any solvent, we always obtained 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline (*VI*) exclusively. The same product is obtained when a similar reaction with 3-phenyl-3-cyano-2-oxopropanoate in tetrahydrofuran is carried out[5]. Both last mentioned reactions show the low stability of keto esters even towards the weakly nucleophilic aromatic *ortho* diamine. In contrast to ester *III* lactone *VII* affords the expected hydrazide[3].

We also submitted to hydrazinolysis 2-ethoxalylmethylene-4-methyl-3-oxo--1,2,3,4-tetrahydroquinoxaline (*VIII*) existing in enamine form[6]. We obtained as a product 1,3-dimethyl-1,2-dihydro-2-oxoquinoxaline (*IX*). The hydrazinolysis takes place on the keto carbonyl group, while hydrolysis takes place at the carbonyl of the ester group[7]. In the preparation of ester *VIII* from dimethyl derivative *IX* and ethyl oxalate we used sodium hydride and we achieved better results in comparison with the procedure described in literature[7].

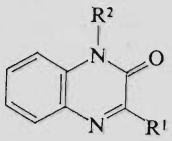
Hydrazino derivative *II* was submitted to the reaction with nitrous acid, accompanied by cyclization, affording 4,5-dihydro-4-oxotetrazolo[1,5-*a*]quinoxaline (*X*) (ref.[2]). On reaction with methyl iodide and isopropyl chloroacetate 5-methyl (*XI*) and 5-isopropoxycarbonylmethyltetrazolo[1,5-*a*]quinoxaline (*XII*) were formed, respectively. The reaction with isopropyl chloroacetate was carried out in the presence of sodium iodide, so that the actual alkylation reagent was iodo acetate. Isopropyl chloro acetate alone does not react, while chloroaceticacid does not react even in the presence of iodide.

For the preparation of tetrazoloquinoxaline analogue of ester *I* we took ethyl (3-chloro-2-quinoxalinyl)acetate[3] as the starting material, which was reacted with sodium azide in ethanol to give a product which absorbed in the carbonyl region of its IR spectrum at the 1 742, 1 660 and 1 640 cm^{-1} bands. The value of the wavenumber 1 742 cm^{-1} does indeed correspond to the unconjugated ester group, but the ketimine tautomeric form is excluded both by the band of ν(N—H) at 3 225 cm^{-1} and the pair of very intensive bands at 1 660 and 1 640 cm^{-1}. Their wavenumbers and the ratio of intensities do not change substantially in the spectra of substances dissolved in tetrachloromethane and chloroform; in tetrachloromethane the wavenumber for ν(C=O) of the first band increased by 11 cm^{-1}. Therefore, this band belongs to the ester carbonyl and the two further bands belong to less polar bonds. This indicates the enamine structure and therefore the product is 4-ethoxycarbonylmethylene-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline (*XIII*). The value of the wavenumber for ν(C=O) 1 742 is higher by about 100 cm^{-1} in comparison with the corresponding value of enamine ester *I*. A possible explanation consists in the electro-

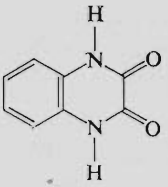
negativity of the tetrazolo ring[8] which withdraws the electrons from the ester group carbonyl more than the amide carbonyl of ester *I*. Our ester *XIII* can be considered as a vinylogue of 1-ethoxycarbonyl- or 1-acyltetrazole which display high wavenumbers for ν(C=O). The pair of the two very intensive bands may be due to the vibrational coupling of this group in the conjugated system with the tetrazole ring. We also determined the enamine structure from the ^{1}H-NMR spectrum; derivative *XIII* in dimethyl sulfoxide contained 90% of enamine.



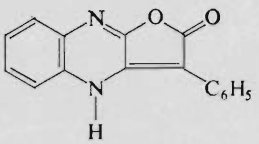
I, $R^1 = COOC_2H_5$, $R^2 = H$
VIII, $R^1 = COCOOC_2H_5$, $R^2 = CH_3$



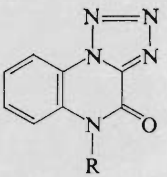
II, $R^1 = NHNH_2$, $R^2 = H$
III, $R^1 = CH(C_6H_5)COOC_5H_2$, $R^2 = H$
IV, $R^1 = CH(CH_3)COOC_2H_5$, $R^2 = H$
V, $R^1 = CH(CH_3)CONHNH_2$, $R^2 = H$
IX, $R^1 = R^2 = CH_3$



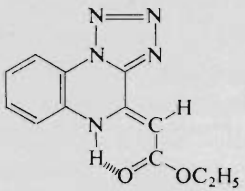
VI



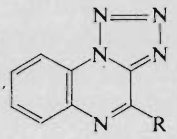
VII



X, R = H
XI, R = CH_3
XII, R = $CH_2COOCH(CH_3)_2$



XIII



XIV, R = $CH(C_6H_5)COOC_2H_5$
XV, R = $CH(CH_3)COOC_2H_5$
XVI, R = $CH_2CONHCH_2CH_2OH$
XVII, R = CH_3

Using a procedure similar to that used in the preparation of ester *XIII* we obtained tetrazole analogues of esters *III* and *IV*, displaying a single band at 1 725 and 1 745 cm^{-1}, respectively, in the carbonyl region. The values for ν(C=O) are close to the carbonyl frequencies of esters *III* and *IV* and they prove the ketimine structure of ethyl (tetrazolo[1,5-*a*]quinoxalin-4-yl)phenyl acetate (*XIV*) and ethyl 2-(tetra-

zolo[1,5-*a*]quinoxalin-4-yl)propanoate (*XV*). N-(2-hydroxyethyl)tetrazolo[1,5-*a*]-quinoxalin-4-ylacetamide (*XVI*), obtained from ester *XIII* and 2-aminoethanol also has the ketinime structure.

The IR spectra of tetrazolo[1,5-*a*]quinoxalines *X*–*XVI* were compared with the spectra of corresponding quinoxalines, and 4-methyltetrazolo[1,5-*a*]quinoxaline[1] (*XVII*) was included into the measurements. The diagnostically most important band is that at 1 515–1 530 cm^{-1} the wave-number of which corresponds to the order of the tetrazole ring bonds. Further bands of medium intensity at ~1 430, ~1 340, 1 240 and 1 220 cm^{-1} were detected only in the spectra of ketimine derivatives. Both last mentioned values are in the region of the wave-numbers of the bands published for tetrazol[9].

4-Oxo derivative *X* displays two bands, for ν(C=O) and ν(N—H), while its N-methyl derivative *XI* displays a single carbonyl band only. The splitting is very probably connected with the association of the molecules of derivative or with Fermi resonance *X*, but the explanation of the doublet by Fermi resonance could not be checked, owing to poor solubility. Tautomeric isomerization is not concerned and the deviation from coplanarity under the effect of substitution on the nitrogen in the position 5 is not operative either, since both derivatives *X* and *XI* possess similar electronic spectra. Derivatives *X*–*XIII*, *XVI* and *XVII* were tested for their herbicidal activity but their effect was low in comparison with Monuron (N-(4-chlorophenyl)-N',N'-dimethylurea) as standard.

EXPERIMENTAL

The melting points were determined on a Kofler block. The IR spectra of compounds in nujol were measured on a Spektromom 2000 instrument and the wave-numbers were calibrated using polystyrene as standard. The mass spectra were measured on a Jeol DS 100 spectrometer, the ^{1}H-NMR spectra on a Tesla BS 487 B instrument at 80 MHz in ($^2H_6$) dimethyl sulfoxide.

Hydrazinolysis of Ethyl (3,4-dihydro-3-oxo-2-quinoxalinyl)phenyl acetate (*III*)

3·1 g (0·01 mol) of ester *III* and 20 g of hydrazine hydrate (80%) were refluxed for 2 h. The mixture was concentrated *in vacuo* and dried over phosphorus pentoxide at 100°C. The residue was extracted with two 10 ml portions of boiling water and the extract was filtered with charcoal. The filtrate was evaporated and the residue crystallized from cyclohexane–ethyl acetate 2 : 1, affording a crystalline product of m.p. 112–115°C, identical according to its m.p. and IR spectrum with an authentic specimen of phenylacethydrazide[10]. The residue after extraction of phenylacethydrazide was recrystallized from 1-butanol and it was identical according to its m.p. and IR spectrum with an authentic sample of hydrazino derivative *II* (ref.[2]).

2-(3,4-Dihydro-3-oxo-2-quinoxalinyl)propanehydrazide (*V*)

A mixture of 1·1 g of ester *IV* (0·0045 mol) and 10 ml of hydrazine hydrate (80%) was refluxed for 4 h. After cooling crystals were obtained with m.p. 240°C (decomp.). IR spectrum: ν(N—H)

3 300, ν(C=O) 1 670, 1 645 cm^{-1}. For $C_{11}H_{12}N_4O_2$ (232·2) calculated: 56·89% C, 5·21% H, 24·13% N; found: 56·86% C, 5·37% H, 24·35% N.

1,2-Dihydro-1,3-dimethyl-2-oxoquinoxaline (*IX*)

2·74 g (0·01 mol) of ester *VIII* were refluxed with 10 ml of hydrazine hydrate (80%) for 1 h. The isolated product was crystallized from 10% ethanol. Yield, 1·5 g (86%) of crystals with m.p. 81—83°C, identical according the m.p. and IR spectra with an authentic sample[11].

4,5-Dihydro-5-methyl-4-oxotetrazolo[1,5-*a*]quinoxaline (*XI*)

A mixture of 5 g (0·027 mol) of derivative *X*, 5 g (0·03 mol) of anhydrous potassium carbonate and 3 ml of iodomethane (0·048 mol) in 100 ml of acetone was refluxed for 8 h. After cooling the precipitated material was extracted by boiling with 100 ml of acetone and the combined acetone solutions were concentrated to 50 ml. After addition of 300 ml of water the precipitated product was filtered off under suction and washed with water. After double crystallization from dioxane 4·5 g (90%) of crystals were obtained, m.p. 242—243°C. UV spectrum: λ_{max} 217 nm (ε = 29 800), 241 (11 400), 253 (11 600), 316 (8 300). IR spectrum: ν(C=O) 1 679 vs, skeletal vibrations at 1 520 w, 1 437 m, 1 343 m, 1 254 m, 1 210 m cm^{-1}. From derivative *X*, UV spectrum: λ_{max} 217 nm (ε 23 080), 241 (8 900), 253 (9 840), 313 (7 940). IR spectrum: ν(N—H) 3 200 m, 3 130 m, ν(C=O) 1 728 vs, 1 678 vs, skeletal vibrations: 1 530 m, 1 437 vs, 1 345 m, 1 251 m, 1 213 m cm^{-1}. For $C_9H_7N_5O$ (201·2) calculated: 34·81% N; found: 34·66% N.

Isopropyl (4,5-Dihydro-4-oxotetrazolo[1,5-*a*]quinoxalin-5-yl)acetate (*XII*)

5 g (0·027 mol) of derivative *X*, 8·02 g (0·05 mol) of anhydrous potassium carbonate, 5·5 g (0·04 mol) of isopropyl chloro acetate and 6·08 g (0·04 mol) of sodium iodide were refluxed for 1 h. After filtration off of inorganic material and concentration of the filtrate 5·95 g (78%) of a product were obtained that melted at 165—170°C. After crystallization from 1-propanol m.p. 169—172°C. IR spectrum: ν(C=O) 1 741 vs, 1 708 vs, skeletal vibrations at 1 520 m, 1 435 m, 1 340 m, 1 260 m cm^{-1}. For $C_{13}H_{13}N_5O_3$ M^+ = 287.

4,5-Dihydro-4-ethoxycarbonylmethylenetetrazolo[1,5-*a*]quinoxaline (*XIII*)

A suspension of 7·8 g (0·12 mol) of sodium azide, 131 ml of 0·1M-HCl and 27 g (0·11 mol) of ethyl-3-chloro-2-quinoxalinylacetate[3] in 46 ml of ethanol was refluxed for 4 h. The precipitated product was crystallized from ethanol to give 5·7 g (25·3%) of crystals, m.p. 122—127°C. On concentrating the ethanolic solution the yield can be increased to 80%. ^{1}H-NMR spectrum: 1·35 t, OCH_2CH_3; 4·23 d, OCH_2CH_3; 4·51 s, CH_2, ketimine; 5·69 s, CH=, enamine. For $C_{12}H_{11}N_5O_2$ (257·2) calculated: 56·02% C, 4·31% H, 27·23% N; found: 55·89% C, 4·38% H, 27·50% N.

Derivative *XIV* was prepared in the same manner from ethyl (3-chloro-2-quinoxalinyl)phenylacetate[3] in a 51% yield, m.p. 133—135°C. IR spectrum: skeletal vibrations 1 515 m, 1 428 m, 1 345 m, 1 260 m cm^{-1}. For $C_{18}H_{15}N_5O_2$ (333·3) calculated: 64·85% C, 4·54% H, 21·01% N; found: 64·80% C, 4·35% H, 20·73% N. Derivative *XV* was obtained in the same manner from ethyl 2-(3-chloro-2-quinoxalinyl)propanoate[12] in a 78% yield, m.p. 96—98°C. IR spectrum: skeletal vibrations 1 515 m, 1 422 w, 1 350 m, 1 245 m, 1 220 m cm^{-1}. For $C_{13}H_{13}N_5O_2$ (271·3) calculated: 57·56% C, 4·83% H; found: 57·46% C, 5·08% H.

N-(2-Hydroxyethyl)tetrazolo[1,5-*a*]quinoxalin-4-ylacetamide (*XVI*)

3·7 g (0·014 mol) of ester *XIII* and 5 ml of 2-aminoethanol were heated at 130°C for 30 min. After cooling the mixture was diluted with water, the precipitated product was filtered off under suction, washed with three 50 ml portions of water and dried. Yield, 2·7 g (74·5%) of the product, m.p. 205—208°C, which did not change after crystallization from dimethylformamide. IR spectrum: ν(N—H) 3 470 m, 3 320 msh, ν(C=O) 1 638 vs, skeletal vibrations 1 520 msh, 1 420 m, 1 352 m, 1 257 m, 1 223 msh cm^{-1}. For $C_{12}H_{12}N_6O_2$ (272·3) calculated: 52·90% C, 4·44% H, 30·87% N; found: 52·70% C, 4·77% H, 31·15% N.

REFERENCES

1. Dreikorn B. A., Thibauet T. D.: US 3 379 387 (1976); Chem. Abstr. *86*, 55 487 (1977).
2. Cheeseman G. W. H., Rafiq M.: J. Chem. Soc. (C) *1971*, 452.
3. Klicnar J., Hájek M., Hoffmann J., Večeřa M.: This Journal *36*, 262 (1971).
4. Toman J., Štěrba V., Klicnar J.: This Journal *46*, 2104 (1981).
5. Moffitt M., Schultz H. P.: J. Org. Chem. *42*, 2504 (1977).
6. Mondelli R., Merlini L.: Tetrahedron *22*, 3253 (1966).
7. Cook A. H., Naylor R. G.: J. Chem. Soc. *1943*, 397.
8. Bellamy L. J.: Spectrochim. Acta *13*, 60 (1958).
9. Lieber E., Enkoji T.: J. Org. Chem. *26*, 4472 (1961).
10. Curtius T., Boetzelen E.: J. Prakt. Chem. *64*, 314 (1901).
11. Cook A. H., Perry C. A.: J. Chem. Soc. *1943*, 394.
12. Toman J., Klicnar J., Macháček V.: This Journal *42*, 529 (1977).

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